The
RANSOHOFF
Memorial Volume
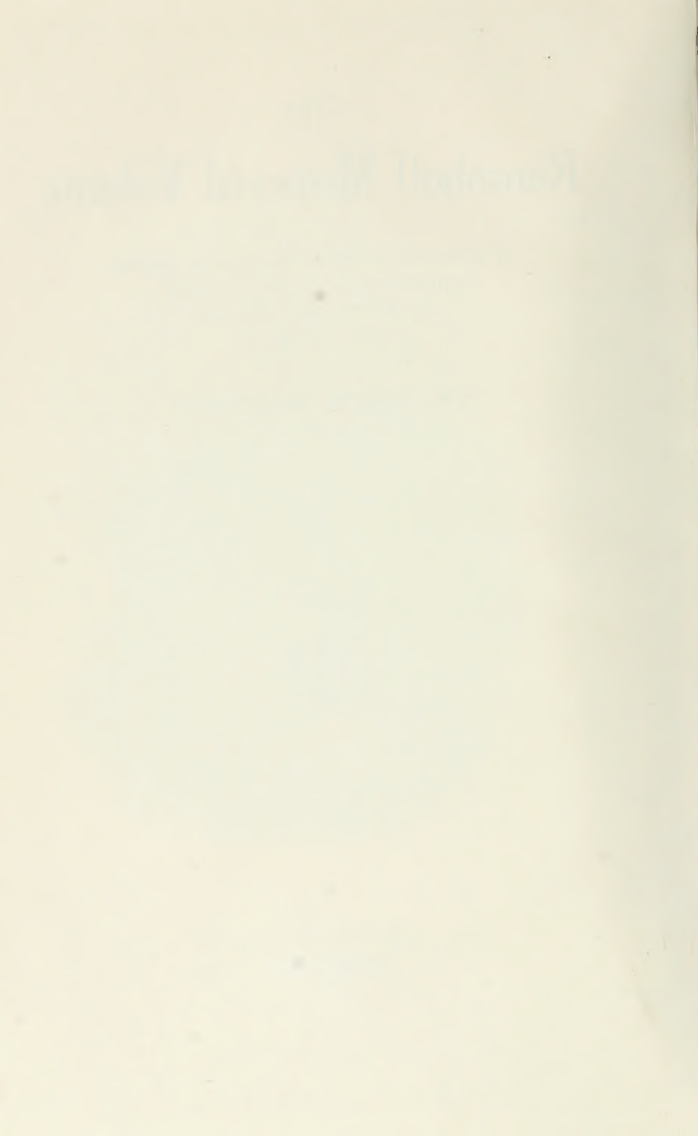
The

Ransohoff Memorial Volume

A Collection of Papers Representing Original
Contributions to the Art and Science
of Medicine by Colleagues
and Students of

DR. JOSEPH RANSOHOFF,

M.D., F.R.C.S. (Eng.), F.A.C.S., LL.D,

Nos Salutamus Nos Recentissime Mortuos

AETERLINCK, in one of his most inspired plays, has originated a very beautiful conception of the hereafter. He believes that far away in the Realms of the Infinite, a man's spirit lives again each time that his name is recalled or spoken here below. Man's immortality rests upon the memories of him that linger in the thoughts of men.

If there be truth in this answer to the greatest of all questions, then the spirit of the man in whose honor this book has been written, will live on in the golden sunlight of the great love that he left in the hearts of his fellow-men. There was about him a singular magnetism, a quality of lovableness that was irresistible. Men talked to him, told him their thoughts and he listened, and when they left him, although he had made no effort, they felt they had won a new and very valuable friendship. He had a deep, warm love for humanity, and each man's life and each man's happiness was worth his own personal effort to guard against harm.

Though for over four decades he practiced surgery, he never became callous to the sight of human suffering. He believed that the highest duty of the doctor was to alleviate pain. With countless hundreds he walked through the Valley of the Shadow of Death and when he emerged with them into the glory of the sunshine once more, he had their lasting confidence and friendship. He will live in the thoughts of these people as he was to them in their hour of trial, the healer and the friend.

He loved youth and the wholesome out-of-door pleasures of youth. His happiest summers were passed with a band of young men in the Canadian woods, where he tramped and fished and smoked and read and cooked marvelous fish chowders for an enthusiastic group of hungry youngsters. To watch him hook and play and land a huge "musky" with those delicate surgeon's hands of his was a treat for a true sportsman. And because he knew and loved and understood the ways of youth he was able to impart to young men the difficult art of his beloved profession as few have been able to teach it. His bedside clinics were invested with a flash of genius. His teachings meant more to his pupils than the dry accumulation of facts necessary to pass examinations and make a livelihood. They meant the handing on of a sacred trust from the old generations to the new. So he will live in the hearts of the men he taught, revered by them as the great teacher who loved and understood them.

In the store-house of his mind lingered fragments and bits of prayers from the old, old faith of his forefathers. Many an old patriarch with sorrow-clouded eyes, lying lonely and suffering in the wards, would brighten into happiness when this man, in passing his bed, would stop to wish him well or whisper a time-worn phrase in the dialect of his own people.

He loved the beautiful things of life, books, music, nature. But, above all else, he loved with a fierce intensity the work to which he devoted the years and strength of his manhood. Before he died, he, who had given the world so much, said: "I have had a perfect life; the world owes me nothing."

When he died the highest and the most obscure sent messages telling of the loss they had sustained in his passing.

He had a great mind and a gentle soul. The world is richer for his having lived.

Contents

CONTENTS—Continued.

CONTENTS—Continued.

Editors' Preface

IN an effort to express to Dr. Joseph Ransohoff their appreciation of his place in the science and art of Medicine a group of his former students determined to issue a volume containing papers consisting of original contributions to the advancement of Medicine by his students and colleagues. This was in June, 1920. The death of Dr. Ransohoff prevented the presentation of this book to him personally, but the publication was continued as a Memorial Volume.

The Editors wish to express their appreciation to the many friends of Dr. Ransohoff for the help they have given in making this work a reality, and to the S. Rosenthal & Co. for their part in the printing of this book. Recognition is given to the publishers of the different articles for permission to reprint them in this book.

To Dr. Joseph Ransohoff

Anatomist, Surgeon, Scholar, Friend and Teacher; to you is dedicated this book. But above all to you as teacher. Eminent in all of your undertakings, as teacher have you been pre-eminent, and the men who throughout forty-two years have known you thus, inscribe to you this tribute of affection and of homage.

Friend and Teacher: the hope had been cherished to present to you this enduring token, while your eye was still undimmed and your tongue still able to serve in its way, inimitable. Within a few short months Fate has taken from us this great privilege. To the wreath of immortality which you have woven for yourself may we be permitted to add a few leaves. "Memory is a net; one finds it full of fish when he takes it from the brook; but a dozen miles of water have run through it without sticking." Therefore, let us, your friends and pupils, wander gently through the years which you have spent, that for us and those who come after us they may have an imperishable record.

May 26, 1853 --- March 10, 1921

For sixty years has stood the church of the Franciscan Fathers in Cincinnati. For sixty years has the grimy figure of St. Francis of Assisi looked down upon Liberty street; venerated by many devout passersby, but also the butt of many a jest from the mischievous boys, who, throughout many years, found in the narrow street below their only playground. To the east a garden, closed in by a high brick wall, separates the church from Vine street; even now, after the passing of two generations of men, a fairly busy thoroughfare, it was formerly very different in its aspect. Abounding in many small shops, the street is, in the daylight hours, perhaps not greatly changed in appearance. The dethronement of King Gambrinus has, however, played havoc with its nocturnal glory. Here we are almost at the northern terminus of that region for so many years gaily spoken of as "Over the Rhine." And it was so spoken of not merely in gayety, but also most aptly; in its houses and in those of the contiguous streets lived a populace prevailingly German. Few, indeed, were the persons one might have encountered here sixty years ago who would have failed to comprehend a German salutation, and fewer still, those who would have failed to respond to it politely and respectfully. In place of the brilliant electric il-

lumination of our time, emphasized by the gaudy resplendence of the "movies" found in every block, we would have found only flickering gas lamps. The many "Bierstuben" with which the street abounded were, for the most part, lighted with oil lamps, and the evening found their tables bearing many glasses of foaming "Lager," behind which sat decent, thrifty and sober men who had wandered from the "Fatherland" long before it went mad with war lust. Some of them, indeed, were forty-eighters, who sought this country in search of liberty and opportunity, and found both. If our imaginations carry us into these rooms with ears as well as eyes, we shall hear serious talk; in this year of 1860 was Abraham Lincoln elevated to his troublous eminence and the premonitions of the Civil War were in the minds and the mouths of men. Then, from the houses of German Vine street and the many habitations of the neighborhood went forth hundreds of these "German citizens" and their sons to prove with their blood and their lives how real was their allegiance to the Union; just as the sons and the grandsons of these same men have not hesitated to show it again in our day in a manner more telling. For now the enemy had become the same "Fatherland" whence their forebears had been derived.

The church of St. Francis is not a beautiful edifice; quite the contrary. From a facade severely plain there rise two spires, as were there two routes to the empyrean; for if the unmoving hands of the clock in the one are at a quarter before five, those of the other say that it is half past eleven. The western windows of the church give upon a narrow street, called Bremen street until 1918. Then in the spirit of belligerent patriotism the name was changed to the present, Republic street. In an unpretentious brick house on Bremen street, just north of St. Francis Church, lived Nathan Ransohoff, and here was spent the boyhood and youth of his only son and youngest child, Joseph. Nathan Ransohoff came to Cincinnati, almost one hundred years before these lines were written, from Westphalia, where in his family there had been men of culture. If great fame was not theirs, neither were they without local distinction, and a prized possession of Joseph Ransohoff's was the portrait of his uncle, with a decoration upon his breast in token of his successful work among the people with whom he lived. It is interesting that the stranger to this city found here friends in the persons of Jacob and Sarah Workum, natives of Amsterdam, the maternal grandparents of Minnie Workum Freiberg, who many years afterward became Mrs. Joseph Ransohoff.

Folk of a pious Jewish orthodoxy were Nathan and Esther Ransohoff. Content with the modest mercantile success which had come to them, they were also satisfied to live quietly in the shadow of St. Francis Church, with its mute and unintentional suggestion that there is more than one way to that realm which, for mortals, is impenetrable and unknowable. Here played the boy, "the hope of the name." He had been intended for the rabbinate by his parents, and with this in view there was laid the foundation

for extended training in Hebrew lore and tradition which had an effect upon his mind and character, enduring to the last and which often occasioned surprise to those who were themselves thus learned. The public school of the neighborhood and Woodward High School gave him all that he received of systematic secular training. After his graduation from high school, in 1870, he passed directly into the study of medicine. The Medical College of Ohio, from which he was graduated in 1874, was one of the best known medical schools of the country of that day, as well as one of the largest. Graham, Blackman, M. B. Wright, Reamy and Bartholow, these were the men who inspired the young medical student with high ideals of medical pedagogy and of scholarship. Of these none exercised a more potent and lasting influence than Graham, and I have heard Ransohoff say, more than once, that in all of his student wanderings he had met with no more brilliant or gifted teacher; his style of teaching he characterized as "histrionic." In my mind's eye I see the father Ransohoff returning to his simple home from the synagogue on the Sabbath eve (Friday) of February 27, 1874. I see him celebrating the Sabbath meal in its traditional beauty; I see the family walking the long way down Vine street to Fourth; I see them seated in Pike's Opera House, where the commencement exercises of the Medical College of Ohio were held. But above all, I see the pride in the faces of mother and father as they see their son, the youngest of the class, called forth to receive the gold medal from the hand of Thaddeus A. Reamy for his essay on Puerperal Eclampsia. How singular, perhaps in no branch of his profession was he afterward destined to have a less active interest than in obstetrics. Before his graduation he had already served as intern in the Cincinnati Hospital; he has told me that the degree of M. D. was conferred only after the year of internship in order to hold the young men in the hospital. The food was so poor that defections before the end of the term could not be otherwise prevented.

After his graduation he proceeded to Germany for graduate study, and it was his father's wish that he should obtain a European degree. Wurzburg, Berlin, Vienna, Paris and London, these were the places of abode and earnest study until his return to Cincinnati in 1877. Kolliker, Virchow Langenbeck, Billroth, Tillaux, Paget and Jonathan Hutchinson; Hebra, Rokitansky and Gerhardt, these are the names of men often spoken of by Ransohoff by reason of the influence which they had exerted upon his development, both as practitioner and as teacher. Having proceeded to London, Ransohoff applied himself energetically to preparation for the examination for Membership of the Royal College of Surgeons of England. This was the degree which he hoped to bring back in response to his father's wish. The difficulty lay chiefly in extremely rigid tests in anatomy; the Fellowship degree seemed altogether beyond possibility in its demand for the utmost in the way of anatomical and surgical knowledge. It was practically never taken until at least one year after the Membership had been conferred, and it seemed time to return to America and to take up

the pursuit of the practice for which he had been so long and so arduously preparing. The M. R. C. S. was given him in April, 1877. Some days afterward, while working in the wonderful Hunterian Museum, he was recognized by Sir James Paget; he complimented him upon his brilliant examination and urged him to try for the Fellowship. This resulted in his obtaining the greatly coveted F. R. C. S. in June, 1877, under conditions almost, if not altogether, unprecedented. Immediately thereafter Ransohoff returned to Cincinnati.

Heralded by this remarkable accomplishment, it was easy for him to obtain recognition in the Medical College of Ohio. Late in the summer of 1877 he was made Demonstrator of Anatomy and began to teach surgery in the college dispensary. In 1879, the untimely death of the brilliant Landon Longworth made a place for him as Professor of Descriptive Anatomy. Remarkable didactic talent such as Ransohoff possessed insured for him immediate advancement as the opportunities appeared. He soon was made a member of the staff of the Good Samaritan Hospital and began to hold surgical clinics, which were eagerly attended by the students, who were not long in appreciating his unusual ability as a teacher, even as the newcomer to a group made up of men like Dawson, Reamy, Conner, Whittaker and his, as well as our, lamented friend, Frederick Forchheimer. Since 1902 Ransohoff occupied the Chair of Surgery in the Medical College of Ohio and in the University of Cincinnati, with the organization of a veritable university faculty in 1909. It was his privilege to live to see the fulfillment of a prophecy which was made at this time by one who disbelieved in its probability, when he wrote:

"If the lessons of the recent past are heeded, if the ambition of the individual is tempered by love of science and by civic patriotism, if the unit is willing to be absorbed by the totality of the purpose embodied in the whole, then Medical Cincinnati may rise again in all her old-time glory, an imperishable monument to the great Daniel Drake, whose genius hovers about the old town, where Western medicine was born and grew into a vigorous adolescence and heroic manhood."

With the occupation of the new Cincinnati General Hospital came the opportunity for the full flowering of the genius of Joseph Ransohoff as a teacher of clinical surgery, and the climax was reached with the installation of the Medical College in its present magnificent building on the same grounds; it was now possible to do things for the student of medicine not dreamed of when he began his career as teacher. The opportunity which he now had for devoting a greater amount of time to teaching was seized with eagerness; an eagerness which could not have been greater had it been the first chance of his life to show his ability and to establish his reputation. It were entirely fruitless to attempt the analysis of his success as a teacher. A sufficient explanation is found in his enthusiasm and in that of his students. That he had passed the time of life when teachers of medicine commonly relinquish a large part of their work, seeking greater

leisure and relief from routine burdens, was never apparent to him in his own self-consciousness, I am sure. On the contrary, he shrank from the thought that he might live, being no longer a teacher of surgery.

Nature had been very kind to Joseph Ransohoff, not only in giving him an active, clear-thinking brain and a remarkably retentive memory, but with these a pleasing voice, a charm of presence and, above all, a love for what was fine and beautiful. The history of his profession and of the outstanding figures there to be found had an irresistible lure for him; he was therefore learned not only in the technical side of medicine and surgery, but also in the story of its development as art and science. His addresses in this field were not many, but they were, all of them, notable and characterized by grace of diction and charm in the manner of their delivery. That he had both talent and love for literary effort not at all connected with his profession is not as well known as it should be. He wrote a number of stories of distinct merit, but they were not published. Surely the crowning effort of his life, in its relation to the Medical College and to the public, was presented on that delightful November day of 1920, when there was celebrated the centennial of the medical school. Ransohoff's unbounded admiration for Daniel Drake, the great founder, and his personal love for Christian R. Holmes, the great builder, made easy for him the composition of his address, "Drake and Holmes," which completely captivated an audience which overfilled the auditorium of the college building. This was for him a great day, not only in the personal triumph which he achieved, but because there was conferred upon him by his Alma Mater the degree of Doctor of Laws. This was a reward, not too great, for more than forty years of devoted service of high value and conspicuous results. Alas! that it should also have marked his last appearance in that auditorium.

It were superfluous to emphasize here in what high degree Ransohoff was a remarkable and successful practitioner of surgery. In addition to learning, manual dexterity, remarkable clinical judgment and even intuition, he had a grace of manner and a sympathy for those who suffered, which endeared him to his patients, exceedingly. He came into surgery at the beginning of its most active and fruitful period. Change followed upon change, innovation upon innovation, but Joseph Ransohoff was able to pass from the scenes of his labors after a long career of uninterrupted activity, conscious of the fact that he was always, and to the end, abreast of the times, marking with his own feet the forefront of progress.

> "And tho', in this lean age forlorn,
>   Too many a voice may cry
> That man can have no after-morn,
>   Not yet of these am I.
> The man remains, and whatso'er
>   He wrought of good or brave
> Will mould him thro' the cycle-year
>   That dawns behind the grave."

Frater, ave atque vale.

ALBERT H. FREIBERG.

Publications of Dr. Joseph Ransohoff

1879

A Contribution to the Study of the Operation for Hare Lip. (Cin. Lancet-Clinic, 1879, v. 3, p. 1-3.)

Tetanus; Nerve Stretching; Cure. (Cin. Lancet-Clinic, 1879, v. 2, p. 41-43.)

1880

Aneurism of the Innominate and Aorta; Ligature of the Carotid and Subclavian Arteries; Death on the Seventh Day. (Am. J. Med. Sc., 1880, v. 80, p. 352-59.)

Hernia of the Abductor Longus. (Cin. Lancet-Clinic, 1880, v. 4, p. 56.)

1881

Erysipelatous Inflammation of the Glottis. (Cin. Lancet-Clinic, 1881, n. s. v. 7, p. 543.)

Permanent Perineal Fistula. (Cin. Lancet-Clinic, 1881, n. s. v. 6, p. 30.)

Rare Cases of Syphilis. (Cin. Lancet-Clinic, 1881, n. s. v. 7, p. 1-4.)

1882

A Contribution to the Surgery of the Liver. (Med. Rec. 1882, v. 22, p. 258-61.)

Ein Beitrag zur Chirurgie der Leber. (Berl. Klin. Wchnschr., 1882, v. 19, p. 600-603.)

Fibroid Polypus of the Rectum. (Cin. Lancet-Clinic, 1882, n. s. v. 8, p. 486.)

Gunshot Injury of the Shoulder. (Cin. Lancet-Clinic, 1882, n. s. v. 8, p. 1-4.)

Tetanus from Injury by Toy Pistol; Stretching of the Median and Ulnar Nerves; Death. (Cin. Lancet-Clinic, 1882, n. s. v. 9, p. 266.)

1883

[Discussion.] (Cin. Lancet-Clinic, 1883, n. s. v. 10, p. 495.)

Early Trephining in Diseases of Bones. (J. Am. Med. Ass., 1883, v. 1, p. 299-302.)

Epithelioma of the Lips. (Cin. Lancet-Clinic, 1883, n. s. v. 10, p. 447-49.)

Papilloma of the Bladder; Operation; Cure. (Med. News, Phila., 1883, v. 42, p. 153-56.)

Retro-Peritoneal Cysto-Sarcoma. (Med. News, 1883, v. 43, p. 575-77.)

The Treatment of Empyema by Pleural Incision; Report of Three Cases. (Cin. Lancet-Clinic, 1883, n. s. v. 11, p. 431-35.)

1884

Sanguineous Cyst of the Neck. (Cin. Lancet-Clinic, 1884, n. s. v. 13, p. 1-4.)

1885

Two Ovariotomies in the Same Patient. (Med. News, 1885, v. 47, p. 115-19. Also reprint.)

Two Ovariotomies Successfully Performed on the Same Patient. (Cin. Lancet-Clinic, 1885, n. s. v. 14, p. 586-91.)

Urethral Calculi. (J. Am. Med. Ass., 1885, v. 5, p. 65-67.)

Urethral Calculi. (Tr. Ohio Med. Soc., 1885, p. 169-73.)

1886

A Case of Aortic Aneurism Treated by the Insertion of Wire. (J. Am. Med. Ass., 1886, v. 7, p. 481-85.)

A Case of Aortic Aneurism Treated by the Insertion of Wire. (Med. News, Phila., 1886, v. 48, p. 597-602.)

A Case of Aortic Aneurism Treated by the Insertion of Wire. (Phila., 1886, 18p., 12°. [Repr. from Med. News, 1886.])

Tracheotomy; a Report of Nine Cases. (Med. & Surg. Reporter, 1886, v. 54, p. 260-62.)

Tracheotomy in Diphtheritic Croup. (Lancet-Clinic, 1886, n. s. v. 16, p. 95, disc., p. 107.)

1888

Considerations on the Anatomy, Physiology, and Pathology of the Caecum and Appendix. (J. Am. Med. Ass., 1888, v. 11, p. 40-46.)

Gastro Enterostomy; a Clinical Lecture. (Polyclinic, 1889-90, v. 6, p. 229-31.)

Old Bilateral Dislocation of the Elbow, With Report of Two Cases. (Cin. Lancet-Clinic, 1889, n. s. v. 23, p. 143-46; also J. Nat. Ass. Railway Surg., 1889, v. 2, p. 128-31.)

1890

Fractura Basis Cranii. (J. Med. Coll., Ohio, 1890, v. 1, p. 29.)

Valedictory Address. (Lancet-Clinic, Mch. 8, 1890.)

Rupture of Middle Meningeal Artery Without Fracture; Ligature of Common Carotid Artery for Secondary Hemorrhage. (Ann. Surg., 1890, v. 12, p. 116-24.)

Rupture of Middle Meningeal Artery Without Fracture; Ligature of Common Carotid Artery for Secondary Hemorrhage. (Tr. Am. Surg. Ass., 1890, v. 8, p. 167-79.)

Tuberculous Disease of the Tarsus. (J. Med. Coll. of Ohio, 1890, v. 1, p. 85-88.)

Tuberculous Diseases of the Tarsus. (Med. News, Phila., 1890, v. 57, p. 564-67.)

Vaginal Cystolithotomy in a Child. (J. Med. Coll., Ohio, 1890, v. 1, p. 41.)

Abscess of Liver; Hepatotomy. (J. Med. Coll. of Ohio, 1890-91, v. 1, p. 111.)

1891

Aneurism of the Femoral Artery; Deligation of the Superficial Femoral; Cure. (J. Med. Coll. of Ohio, 1891, v. 2, p. 5. Also Cin. Lancet-Clinic 1,891, v. 26, p. 529-31.)

Pistol-Shot Wounds of the Brain. (Cin. Lancet-Clinic, 1891, v. 27, p. 557-61.)

Linear Craniotomy for Microcephalus. (Med. News, June 13, 1891.)

Ruptur der Arteria meningea media ohne Fractur; Ligatur der Arteria carotis communis bei secundärer Blutung. (Arch. f. Klin. Chir., 1891, v. 42, p. 229-36.)

1892

Management of the Gangrenous Hernia, With Report of a Case. (J. Am. Med. Ass., 1892, v. 19, p. 198.)

Traumatic Aphasia. (Ohio Med. J., 1892, v. 3, p. 41-43.)

Treatment of the Gangrenous Hernia. (Ann. of Surg., 1892, v. 16, p. 336-51.)

Trephining for Abscess of the Brain. (Cin. Lancet-Clinic, 1892, v. 29, p. 666-73.)

1893

Empyema. (Tr. Ohio Med. Soc., 1893, p. 285-93. Also Cin. Lancet-Clinic, 1893, v. 31, p. 150-54.)

Recurrent Appendicitis; Laparotomy; Fecal Concretion, With Bullet for Nucleus. (Ohio Med. J., 1893, v. 4, p. 235.)

Report of a Case of Appendicitis. (Cin. Lancet-Clinic, 1893, v. 30, p. 675.)

1894

Extirpation of Aneurisms. (Ann. of Surg., 1894, v. 19, p. 78-84.)

Thyroid Abscess, Thyroidectomy; Recovery. (Ann. of Surg., 1894, v. 20, p. 406-413.)

Strangulated Hernia Gangrene of the Intestine. (Ohio Med. J., 1894, May.)

Treatment of Strangulated Hernia. (J. Am. Med. Ass., 1894, v. 23, p. 20-26.)

1895

Concerning Stone in the Kidney, and Its Operative Treatment. (J. Am. Med. Ass., 1895, v. 25, p. 1-7.)

Injuries and Diseases of the Neck. (Encycl. Surg. (Ashhurst, N. Y.), 1895, v. 7, p. 751-82.)

Nature and Treatment of Glands of the Neck. (Med. Fortnightly, 1895, v. 8, p. 470.)
Pelvic Reflexes in the Male. (Med. Progress, 1895, v. 11, p. 261-64.)
Pelvic Reflexes in the Male. (Am. J. of Obst., 1895, v. 31, p. 675-79.)
Sarcoma of Bone. (Ohio Med. J., 1895, v. 6, p. 25-30.)
Tuberculosis of the Neck. (Ohio Medical Journal, 1895, p. 172-74.)

1896

Large Parosteal Fibro-Sarcoma of the Thigh. (Annals of Surgery, 1896, v. 24, p. 188-195.)
(Whitaker, Ransohoff and Kramer):
Paraplegia; Gunshot Wound of the Spinal Cord; Bullet Located by the Roentgen Ray, and Subsequently Extracted; Obstinate Bed Sores Relieved by Constant Stay in the Water Bath for Three Months. (Inter. Med. Mag., 1896-7, v. 5, p. 647-663.)
Parosteal Sarcoma of the Femur; Extirpation With Recovery. (Tr. Am. Surg. Ass., 1896, v. 14, p. 443-454.)
Susceptibility and Immunity to Surgical Infections. (Ohio Med. Journal, 1896, v. 7, p. 169-172.)
Surgical Treatment of Tubercular Lesion. (Cin. Lancet-Clinic, 1896, v. 36, p. 653-657.)
Ueber Erinnerungstäuschungen bei Alkohol-Paralyse. (Allg. Zeitschr. f. Psychiat. etc., 1896-7, p. 933-943.)
Operative Treatment of Irreducible Subcutaneous Fractures. (Am. Jour. Med. Science, 1897, v. 114, p. 417-424.)

1897

Radical Cure Umbilical Hernia, by Omphalectomy. (Med. Rec., 1897, v. 51, p. 150-52.)
Remarks on Operative Treatment of Irreducible Dislocation of the Shoulder. (Ohio Med. Journal, June, 1897.)

1898

Cancer of the Bladder. (Cin. Lancet-Clinic, 1898, n. s. v. 41, p. 632.)
Lympho-Sarcoma of the Neck. (Cin. Lancet-Clinic, 1898, n. s. v. 40, p. 608-10.)
Considerations on the Diagnosis and Operative Treatment of Gall Stones. (Cin. Lancet-Clinic, 1898, n. s. v. 40, p. 95-104.)

1899

Decortication of the Tongue, in the Treatment of Lingual Psoriasis. (Ann. of Surgery, May, 1899.)
Nephrectomy Versus Nephrotomy. (Tr. Am. Surg. Ass., 1899.)

1900

Our Students and Their Teaching. (Cin. Lancet-Clinic, 1900, n. s. v. 44, p. 479-486.)
Specimen of Vesical Calculus. (Cin. Lancet-Clinic, 1900, n. s. v. 45, p. 615-16.)

1902

Trephining for Brain Tumors; Report of Two Successful Cases, One of Nine Years. (J. of Am. Med. Ass., 1902, v. 39, p. 903-06.)

1903

(Ransohoff, J., and Phelps, A. V.):
An Unusual and Fatal Hemorrhage from Trephining. (Tr. Am. Surg. Ass., 1903, v. 21, p. 563-568.)
Zur Aetiologie der akuten hämorrhagischen Encephalitis. (Monatsch. f. Psychiat. u. Neurol., 1903, v. 13, Ergnzngshft, p. 440-48.)
Hepatectomy Tuberculoma of the Liver. (Tr. South. Surg. & Gynec. Ass., 1903; 1904, v. 16, p. 403-10. Also Med. News, 1904, v. 84, p. 727-730.)

Syphilis am Auge. (Festschr. z. 1st. Cong. d. Deutsch. Gesellsch. z. Bekämpf. d. Geschlechtskrankh., 1903, p. 132-34.)

Unilateral Disease of the Kidney Simulating Stone. (J. of Am. Med. Ass., 1903, v. 40, p. 1502-04. Also Tr. South. Surg. & Gynec. Ass., 1902; 1903, v. 15, p. 364-70.)

1904

Stone in the Kidney, Its Diagnosis and Operative Treatment. (Med. News, 1904, v. 85, p. 1011-15.)

1905

Gangrene of the Gall-Bladder. (Tr. South. Surg. & Gynec. Ass., 1905.)

Renal Calculus Removed from Ureter. (Lancet-Clinic, 1905, n. s. v. 54, p. 558.)

Thyroidectomy in the Treatment of Exophthalmic Goitre; With Report of Cases. (Lancet-Clinic, 1905, n. s. v. 54, p. 673-78.)

1906

Cancer of the Stomach from the Surgeon's Viewpoint. (Lancet-Clinic, 1906, n. s. v. 56, p. 625-29.)

Case of Sarcoma of Head of the Tibia. (Lancet-Clinic, 1906, n. s. v. 56, p. 698.)

Discussion of the Pleura in the Treatment of Chronic Empyema. (Ann. Surg., 1906, v. 43, p. 502-11.)

Cancer of the Stomach from the Surgeon's Viewpoint. (Abstr. Ohio Med. J., 1906-7, v. 2, p. 162-65.)

Gangrene of the Gall Bladder. (Tr. South. Surg. & Gynec. Ass., 1905; Phila., 1906, v. 18, p. 48-68.)

Gangrene of the Gall Bladder, Rupture of the Common Bile Duct, With a New Sign. (J. Am. M. Ass., 1906, v. 46, p. 395-97.)

Pulsating Exophthalmos; Ligature of the Common Carotid, External Carotid and Superior Thyroid Arteries. (Surg. Gynec. & Obst., 1906, v. 3, p. 193-95.)

Rupture of the Common Duct With an Unusual Sign. (Tr. South. Surg. & Gynec. Ass., 1905; Phila., 1906, v. 18, p. 50-68.)

The Treatment of Fractures of the Patella. (J. Am. M. Ass., 1906, v. 47, p. 1177-81.)

1907

Die Behandlung der Patellarbrüche. (Klin. Therap. Wchnschr., 1907, v. 14, p. 127-36.)

Cirrhotic Liver, With Ascites and Albuminuria; Talma Operation Performed, Followed by Relief of Ascites and Albuminuria. (Lancet-Clinic, 1907, n. s. v. 58, p. 355.)

Very Large Recurrences After Operation for Carcinoma of the Breast. (Ann. Surg., 1907, v. 46, p. 72-80.)

Very Late Recurrences After Operation for Carcinoma of the Breast. (Tr. Am. Surg. Ass., 1907, v. 25, p. 187-95.)

1908

A New and Rapid Method of Perineal Drainage in Suprapubic Prostatectomy. (J. Am. M. Ass., 1908, v. 51, p. 887-90.)

Surgery of the Kidney, the Ureter and the Suprarenal Gland. (Syst. Surg. (Keen), 1908, v. 4, p. 183-271.)

Venous Thrombosis and Hydrocele of the Inguinal Canal. (Ann. Surg., 1908, v. 48, p. 247-57. Also Tr. South. Surg. & Gynec. Ass., 1907; Phila., 1908, v. 20, p. 406-17.)

1909

Gunshot Injury of the Brain, With Late Manifestations After Immediate Recovery. (Ann. Surg., 1909, v. 50, p. 66-72. Also Tr. Am. Surg. Ass., 1909, v. 27, p. 586-94.)

Renal Surgery. (Toledo M. & S. Reporter, 1909, v. 35, p. 49-55.)

Kidney Surgery—Oration. (Ohio State M. J., Jan., 1909.)
Inter-Ilio-Abdominal Amputation, with Report of a Case. (Ann. Surg., 1909, v. 50, p. 925-35.)

1910

The Modern Surgery of the Kidney. (West. Virg. M. J., 1910-11, v. 5, p. 329; 63.)
Pancreatic Hemorrhage and Acute Pancreatitis. (Surg. Gynec. & Obst., 1910, v. 10, p. 208. Also Ann. Surg., 1910, v. 51, p. 670-81.)
Pancreatic Hemorrhage and Acute Pancreatitis, With a Report of Three Cases. (Tr. South. Surg. & Gynec. Ass., 1909; Phila., 1910, v. 22, p. 112-25.)
Prognosis and Operative Treatment of Fracture of the Base of the Skull; Based on an Analysis of 190 Cases. (Ann. Surg., 1910, v. 51, p. 796-811. Also Tr. Am. Surg. Ass., 1910, v. 28, p. 560-77.)

1911

(Ransohoff, J., and Ransohoff, J. L.) :
Intrathoracic Surgery (Heart and Oesophagus Excluded). (Am. Pract. & Surg. (Bryant & Buck), 1911, v. 8, p. 3-58.)

1912

The Dissecting Room; Then and Now. (Lancet-Clinic, 1912, v. 107, p. 426.)
Gastro-Enteroptosis; When Is Surgery Indicated? (Surg. Gynec. & Obst., 1912, v. 15, p. 21-27.)
Ice Tongs Extension for Simple Fracture of the Femur. (Tr. Am. Surg. Ass., 1912, v. 30, p. 706-38. Also Lancet-Clinic, 1912, v. 108, p. 179-82.)
Median Harelip. (Lancet-Clinic, 1912, v. 108, p. 485-87.)
The Operative Treatment of Gastro-Enteroptosis. (Bost. M. & S. J., 1912, v. 167, p. 347-58.)
Acute Unilateral Septic Infarct of the Kidney. (Lancet-Clinic, v. 1912, 107, p. 583.)
Suture of Bullet Wound of the Lung with a New Method of Closing Pleural Defects. (Lancet-Clinic, 1912, v. 107, p. 517-19.)

1913

Acute Perforating Sigmoiditis in Children. (Ann. Surg. 1913, v. 58, p. 218-25. Also Tr. Am. Surg. Ass., 1913, v. 31, p. 422-30.)
Fat Hernia. (Lancet-Clinic, 1913, v. 19, p. 6-10. Also Tr. South. Surg. & Gynec., 1912; Phila., 1913, v. 25, p. 260-74.)
Osteitis Deformans, Central Sarcoma, Streptococcus Infection. (Lancet-Clinic, 1913, v. 110, p. 672-74.)
What Can Surgery Do for Gastro-Enteroptosis? (Tr. South. Surg. & Gynec. Ass., 1912, v. 24, p. 564-76 [Discussion], p. 590-602.)

1914

Heredity in Bone Lesions, With the Report of an Unusual Family History. (Tr. South. Surg. & Gynec. Ass., 1913; Atlanta, 1914, v. 26, p. 166-70.)
(Ransohoff, J., and Ransohoff, J. L.) :
Radium Treatment of Cancer. (Lancet-Clinic, 1914, v. 111, p. 661-70.)

1915

Pancreatic Cyst as a Cause of Unilateral Hematuria With Report of a Case. (Tr. South. Surg. & Gynec. Ass., 1915, v. 28, p. 119-29.)
Status of Cerebral Surgery. (Cin. Lancet-Clinic, 1915, v. 113, p. 537-41.)

1916

Addresses on Daniel Drake. (Lancet-Clinic, 1916, v. 115, p. 599-609.)
Angina Ludovivi. (Lancet-Clinic, 1916, v. 115, p. 431-34.)

Dislocation of the Knee. (Lancet-Clinic, 1916, v. 115, p. 69-71. Also Tr. West. Surg.
    Ass., 1915; Minneap., 1916, p. 8486.)
Pancreatic Cyst as a Cause of Unilateral Haematuria With Report of a Case. (Surg.
    Gynec. & Obst., 1916, v. 22, p. 275.)

(Ransohoff, J., and Ransohoff, J. L.) :

Radium Treatment of Uterine Cancers. (Ann. Surg., 1916, v. 64, p. 298-303. Also
    Tr. Am. Surg. Ass., 1916, v. 34, p. 202-12.)
Radium Treatment of Uterine Fibroids. (Lancet-Clinic, 1916, v. 115, p. 116-18.)
A Simple Method of Draining Empyema. (J. Am. M. Ass., 1916, v. 66, p. 1196.)

1917

Congenital Lipomata of the Cheek. (Ann. Surg., 1917, v. 65, p. 711-14. Also Tr.
    South. Surg. Ass., 1916; Phila., 1917, v. 30, p. 65-69 [Discussion], p. 80-85.)
Plastic Surgery. (Ref. Handb. Med. Soc., 1917, v. 7, p. 240-253.)
Some Considerations in Brain Surgery. (Interstate Med. J., 1917, v. 24, p. 343-53.)

1918

Hemorrhage from an Aneurism of the Internal Carotid Artery, Following Septic Sore
    Throat. (Ann. of Surgery, 1918, v. 68, p. 152-55. Also Tr. Am. Surg. Ass.,
    1918, v. 36, p. 456-60.)
On Injuries of the Cervical Spine. (Tr. South. Surg. Ass., 1918, v. 21, p. 265-282.
    Also Surg. Gynec. & Obstet., 1918, v. 27, p. 241-47.)
Teaching in the Hospital. (Interstate M. J., 1918, v. 25, p. 749-53.)

1919

Traumatic Facial Diplegia. (Ann. of Surgery, 1919, v. 70, p. 150-56.)

1920

Empyema at Cincinnati General Hospital During Influenza Epidemic. (J. of Am.
    Med. Ass., 1920, v. 74, p. 238.)
Hyperplastic Tuberculosis of Small Intestine. (Ann. of Surgery, 1920, v. 72, p. 97-103.)
John Hunter. (Cin. Journal of Med., 1920.)
On the Borderland of Medicine and Surgery. (Med. Bull. University of Cin.,
    Nov., 1920.)

EVA G. KYTE.
ANNA J. DULING.
MARGARET MURRAY.

THE THERAPEUTIC POSSIBILITIES OF BLOOD TRANS-
FUSION—METHODS, INDICATIONS AND RESULTS*

E. R. Arn, M. D., F. A. C. S.
Junior Surgeon, Miami Valley Hospital.

HISTORICAL CONSIDERATION.

The operation of blood transfusion is an ancient one. Mention of it may be found in early medical writings. In early times it was attempted by using blood of lower animals. It was not until after the discovery of the circulation by Harvey, in 1628, that it was taken up with added interest, as well as along scientific and rational lines. Dr. J. B. Dennis, professor of physiology at the University of Paris, successfully performed the first transfusion of human blood to a patient in 1667. This was done by means of a bone canula.[1]

The Germans used defibrinated blood quite extensively in the early part of the nineteenth century. But because of the dangers of intravesical clotting, it was given up, and use of saline solution substituted.

The modern practice of blood transfusion may be said to have had its origin in 1897, when Murphy reported his method of blood vessel suture in transfusion. In 1906, George W. Crile,[2] reported his special canula for transfusion. It was a marked advance in this work.

The difficulties and objections to all of these methods were the, (a) wound on the donor; (b) obliteration of important blood vessels; (c) and difficulties encountered in technique.

Further investigation developed the syringe method, Lindeman,[3] the paraffined tubes of Kimpton and Brown[4]; the syringe method of Unger,[5] and finally the anticoagulants of Lewishon.[6] The simplest as well as the most practicable of all of these is the anticoagulant or Citrate method, and is the method of choice in the majority of clinics today.

TECHNIQUE OF CITRATE METHOD.

The citrate method is the method in general use today. The apparatus necessary consists of the following:

  1 Tourniquet.
  4 Intravenous needles (Kaliski type).
  4 Pieces of rubber tubing, 12 inches long.
18 Grains of sodium citrate.
  1 30 cc. Graduate.
  1 500 cc. Graduate.
  1 Glass stirring rod.
  1 Glass cylinder with 3 feet of rubber tubing.
  2 or more cambric needles.

The citrate solution is prepared by boiling the citrate in two ounces or 60 cc. of sterile distilled water for two minutes, and 30 cc. or one ounce is placed in the sterile 500 cc. graduate containing the sterile glass stirring rod. The intravenous needle is introduced into the vein of the donor, after transfixing same with a cambric needle, and blood is allowed to flow into the 500 cc. graduate. When nearing the 250 cc. mark, the other 30 cc. or one ounce of citrate solution is added, and blood is permitted to flow until there are 500 cc. of mixture. If more blood is desired, a sufficient amount of citrate solution is added to maintain the ratio of 0.24 per cent., or 30 cc. of 2 per cent. citrate solution for each 250 cc. of blood.

Should clotting occur in the needle of the donor, it should be immediately withdrawn and another inserted.

The citrated blood is then transferred to a suitable flask, and permitted to flow into the vein of the recipient, very slowly at first, especially for the first 60 cc. of citrated blood; marked slowing of pulse, attacks of syncope, precordial distress, dyspnoea, and severe pains in lumbar region are danger signals, and transfusion should be stopped and another donor secured. Except in acute haemorrhage, where the bulk is most important, 500 cc. of mixture is usually all that is required to stimulate the blood-forming organs in chronic conditions.

INDICATIONS OF TRANSFUSIONS.

Hard and fast rules cannot be drawn. One must be guided by the single purpose of doing the most good with the minimum risk. I hardly think that any great number of unnecessary transfusions are carried out, but I am convinced that many cases are lost either by not transfusing at all, or by doing it too late. And not only this, there are many, many cases whose illness could be materially shortened by introduction of blood, whose operation could be made less hazardous, and whose whole aftercourse could be made less burdensome. The following is a list of probable indications:

1. Transfusions for actual haemorrhage:
    (a) Traumatic.
    (b) Gastric and duodenal ulcer.
    (c) Post-partum.
    (d) Ruptured ectopic pregnancy.
    (e) Typhoid haemorrhage.

2. Transfusions in connection with the surgical operations:
    (a) Preliminary to, during and after operation.
    (b) For post-operative haemorrhage.
    (c) For post-operative shock.
    (d) For post-operative anaemia and prostration.

3. Transfusions for the relief of haemorrhagic conditions.
    (a) Purpura haemorrhagica.
    (b) Haemopilia.

    (c) Haemorrhage secondary to (1) blood diseases, (2) severe infections, (3) jaundice, (4) idiopathic uterine.

4. Transfusions for blood disease:
    (a) Pernicious anaemia.
    (c) Leukaemia.

5. Transfusions for infections:
    (a) Infections with pyogenic organisms.
    (b) Subacute streptococcus endocarditis.
    (c) Subacute infection of any nature other than septicaemia.

6. Transfusions for intoxication and poisonings:
    (a) Toxaemia of pregnancy.
    (b) Eclampsia.
    (c) Uraemia.
    (d) Benzol poisoning.
    (e) Illuminating gas poisoning.

7. Transfusions for debilitated conditions:
    (a) Cancer.
    (b) Malnutrition.
    (c) Simple anaemia from any cause.

TRANSFUSION IN RELATION TO HAEMORRHAGE AND OPERATION.

In discussing class one and two, we may briefly discuss other means of controlling haemorrhage. Until the advent of blood transfusion in a practical form, there was no dependable reserve remedy in the physician's armamentarium, so far as great blood losses were concerned, chief among these is the futility of drugs, and next in order is abuse of salt solution. One has only to consult the hospital records to discover how profoundly drugged were most patients who had the misfortune to bleed, and a little closer study of some records will show how thoroughly waterlogged by salt solution they were in addition.

It should be generally understood that if the bleeding has not been too great, a few hundred cc. of salt solution are all that is needed to tide a patient over a dangerous period. In cases of very severe haemorrhage, the amount may be increased a bit, but if 1000 to 1500 cc. of solution do not steady a falling blood pressure, or cause a slight rise, its introduction had better be discontinued. *Even where there has been a rise, the greatest caution must be exercised, for be it remembered that in these desperate conditions, salt solution will frequently cause a rise in blood pressure, but will not sustain it.*

Where the bleeding has been excessive, a transfusion of blood is indicated because it has been conclusively shown that blood alone can raise a pressure and sustain it. Salt solution has no sustaining power, per se, and when the fall comes after a rise from this means, it usually protends the end, for added salt solution is useless. It never raises a pressure twice.

As the result, then, of blood transfusion, we have been able to really study the phenomenon of haemorrhage for the first time, and we have learned the value of doing as little as possible in the condition. Rest, quiet, attempts to check the bleeding by mechanical means, an ice bag over or near the site of bleeding as possible, a bit of morphine for the restlessness occasioned by the condition, and salt solution, and we have the entire armamentarium for treating bleeding. For we have learned that the body itself does more towards checking haemorrhage than can be done by outside means, by automatically lowering its own blood pressure, and thereby causing a slowing of the circulation and renewed opportunity for coagulation of the blood at the site of leakage. But the more I see of haemorrhage and anaemia in general, the more I am convinced of the utter futility of having a specific rule by which to be rigidly governed. Each case is a study into itself; each individual represents an entity which must be judged from all angles, and experience in handling the condition must have a great deal of weight in the ultimate decision as to the course to pursue. It is advisable though to have some tentative plan of procedure in case of haemorrhage, and since there are certain fundamental features common, in a degree, to all cases, it is possible to formulate a working rule. For instance, a sudden loss of blood is a much more serious matter than a gradual depletion, and a rapidly falling blood pressure is always a warning of value, though it must be remembered that nausea of the slightest degree will affect this phase of the situation. But these two features really are dependable guides in the majority of instances, and experience has demonstrated that a good working rule is *to transfuse if the blood pressure falls as low as seventy mm. of mercury, since life is hardly possible with a pressure below that limit.* In some instances, if the physician or surgeon in charge of the case has not taken the steps usual in emergency cases, it may be wise to delay until these can be instituted, preparation for transfusion being made in the interval. If the actual bleeding has been checked, if the patient is quiet, if salt solution has been given in the proper manner, and the blood pressure still remains around seventy, with a tendency to flutter a little below this point, it may be assumed that the case is utterly hopeless, unless new blood is introduced, and procrastination at this stage of the game is a fearfully dangerous plan.

Quoting the late Lindeman,[*] *"in cases of haemorrhage, blood transfusion is specific, no matter how extreme the haemorrhage, provided some life is still present. There is no condition so grave from haemorrhage alone, that a patient cannot be revived by blood transfusion."*

Case Number . Mrs. H. Diagnosis, ectopic pregnancy. Was admitted to hospital for operation. While being prepared, was seized with sharp pain in left side in region of tube, followed rapidly by fainting and collapse. Pulse imperceptible at wrist. Respiration rapid, air-hunger marked. Patient semi-conscious. Operation was rapidly performed under local anaesthesia, bleeding vessel secured, left tube removed. Transfusion was started. Patient became conscious after receiving 300 cc. of blood, pulse perceptible. Was given all told 1,000 cc. of blood from Group II. donor, patient being in Group II. Pulse 120 on leaving table, and made good recovery.

TRANSFUSION FOR HAEMORRHAGIC CONDITION.

Transfusions for haemorrhagic conditions comprise a group of unknown etiology, and whose treatment in the past have run the entire gamut of therapeutics. In Purpura Haemorrhagica, the results of transfusions are only fairly good. Repeated small transfusions are often necessary to control bleeding.

Haemophilia is not cured by transfusion, but for the bleeding of haemophilia it is practically a specific. It will succeed when all other methods fail. Valuable time should not be lost in attempts to control bleeding by other methods, since we have at our command a specific that will not only control bleeding, but replace the blood lost.[9]

In bleeding of the new-born, transfusion is a specific. An almost exsanguinated infant, too weak to cry and in a dying state, is transformed immediately into an apparently healthy, rosy and crying baby. As in haemophilia, it will save the lives of those who are not helped by subcutaneous injections of serum or blood. Temporizing by using less effective measures, may cost the baby's life. This is especially true in cases of melena neonatorum, which are the most serious, because we do not know just when the haemorrhage began, or how much internal haemorrhage is taking place. Just as soon as the diagnosis of bleeding from the stomach or the bowel of the new-born is made, transfusion should be performed.

In jaundice, where the coagulation time is delayed, a transfusion will lessen the danger of bleeding. In cases of obstruction of the common duct, even of long standing with marked jaundice, operation may be successfully performed without haemorrhage or oozing, if a prophylactic transfusion has been made

Case No. ——. Mr. H., age 60. Jaundice of eight weeks' standing. History of repeated attacks of gall-stone colic. Jaundice followed last attack of colic. Was given a prophylactic transfusion of 350 cc. of blood, and operated at end of 24 hours. Several stones were found in the common duct, as well as in gall-bladder. No more than ordinary bleeding during operation; no oozing following. Coagulation time before transfusion 15 minutes. Patient in Group II., and donor in Group IV.

TRANSFUSION FOR BLOOD DISEASES.

Transfusion for blood diseases of this class, *viz.*, pernicious anaemia and leukaemia, may be a life-saving measure in prolongation of the life of the individual. *In pernicious anaemia, transfusion yields results superior to any other mode of therapy. Frequently it acts as a life-saving measure by initiating the onset of a remission.* There is no evidence that the disease may be cured by this method. Repeated transfusions may be necessary, but the lives of many of these individuals can be made useful for years. They should all be grouped, and have at their command suitable donors. Small doses of blood seem to bring about a remission as quickly as large doses. Some donors seem to accentuate a remission sooner than others. In these cases the same donor should be used for subsequent transfusions, as the dose of blood need not be large.

A small percentage of cases of pernicious anaemia do not respond to transfusions, they being of the so-called acute variety.

Case illustrating the so-called chronic variety is as follows:

Case No. ——. Mr. W., aged 52. Diagnosis, pernicious anaemia. Hemoglobin 28 per cent, Sahli. Group II. 1, 950,000 R. B. C. Many normoblasts marked poikilocytosis, dyspnoea and palpatation on least exertion. Began to feel weak 18 months ago, and had to quit his occupation one year ago. Had been in bed most of the time for past two months. Was given 300 cc. of blood at intervals of one week Group IV. donor, for three doses. Marked improvement after first transfusion as evidence by Hb. 40 per cent Sahli., increasing appetite, dyspnoea and palpatation less marked. Hb. 55 per cent after second transfusion, and was able to walk three squares to barber shop. Returned to his home in northern part of state after third transfusion.

In acute lymphatic leukaemia, only a temporarily favorable effect can be secured by transfusion, even though we withdraw a large amount of blood by phlebotomy and make use of a massive transfusion obtained from two donors, or employ repeated transfusions, or carry out transfusions very early in the disease.

Our greatest possibilities for research lie in Class V., or the sub-acute and chronic infections. It has been fully demonstrated by clinical evidence that transfusions in localized pyogenic infections will increase the patient's vitality and aid in overcoming the infections.

In bacteraemia, when the source of the organisms can be found and eliminated, the results are excellent, as in cases of sinus thrombosis following mastoiditis, in which the jugular has been ligated.

Many of our long, drawn out cases of appendiceal abscess and empyemia would be materially shortened by small therapeutic doses of new blood. Examples of this class are the following:

Case No. ——. Mr. D. Diagnosis, secondary anaemia; Hb. 35 per cent, R. B. C. 2,500,000. Operated three months previous, at which time a left nephrectomy was done for pyonephrosis, secondary to renal calculus. Patient has made a very slow and discouraging recovery. Has been unable to work, and was confined to his home. Was given 350 cc. of blood, and ten days later 300 cc. more. After second transfusion, patient was able to be up and care for himself. Returned to his home feeling stronger, and with a Hb. index of 65 per cent.

Case No. ——. Miss A. Diagnosis, chronic empyemia. Cavity of eighteen months duration, holding about 400 cc. Operated second time; Modified Shede operation, patient weak, pulse 116 to 120, and wound discharging large amount of pus. Was given a therapeutic dose of 300 cc. of blood. After two days, patient said she felt much stronger, wound began to show healthy granulation, discharge became less in amount, and pulse rate fell to 88.

Other examples abound, but these are sufficient to indicate the necessity of an awakening on the part of surgeons to certain definite deficiencies in their handling of anaemic, debilitated states secondary to chronic infections. If a person suffers a sudden loss of a great volume of blood, we make up the deficiency by adding fresh blood. Why, then, do we not likewise in the many secondary anaemias, that also suffer blood losses, but in smaller amounts and over longer periods? I have transfused a few of these chronics, and the new blood has done more to restore hope and sleep and appetite than

weeks of rest and barrels of iron and arsenic. I do not decry these necessary adjuvants in the least; on the contrary, I advise their constant use, and have seen splendid results obtained. I merely deprecate and condemn their promiscuous employment in conditions beyond their therapeutic reach. They can do a certain amount of good, but in many cases they are absolutely worthless, and in many of these, one or more blood transfusions will almost produce a miracle, after which the drug and rest-therapy may be judiciously resumed. This has been proved, but has not been recognized.

TRANSFUSION FOR POISONING.

Transfusions in this class are still in the experimental and research stage, except for poisoning from illuminating gas.

This was one of the early fields for blood transfusions, and consists of blood letting and blood giving. These cases are usually bled 700 to 1000 cc. and then transfused a similar amount.[10]

Cases in Class VII., are really a repetition of conditions described earlier in this paper. Kerley, in a recent article, has advised small transfusions in certain non-specific types of Marasmus. He usually gives several doses of not over 30 to 50 cc. at intervals of five to seven days.

DANGERS OF BLOOD TRANSFUSION.

The dangers from blood transfusions can be easily avoided, and the operation made perfectly safe by avoiding the following:

(a) Use of incompatible blood.

(b) Excessively large transfusions.

(c) Emboli of air or blood clot.

Incompatibility of Donor's Blood: Moss[11] has shown the presence in human blood of iso-agglutins and iso-hemolysins. These substances will cause agglutination and hemolysis of the red cells when incompatible bloods are mixed. Moss found that agglutination frequently occurs without hemolysis, but that hemolysis is always associated with agglutination. Human beings can be divided into four groups, depending upon agglutins present in serum, and the capacity of cells to agglutinate. If a transfusion is to be safe, both the donor and the recipient should belong to the same group, or cells of the donor should not be agglutinated by serum of the recipient.

These groups are permanent in their characteristics, and depend upon the Mendelion laws of inheritance.

The following are the four groups with the percentage of individuals in each group:

Group I., 10 per cent. of all individuals contain no agglutins.

Group II., 43 per cent. of all individuals contain agglutin A.

Group III., 7 per cent. of all individuals contain agglutin B.

Group IV., 40 per cent. of all individuals contain agglutin A and B.

RELATIONS OF THE FOUR BLOOD GROUPS.

Group:	I.	II.	Serum. III.	IV.	
I.	o	x	x	x	I.
II.	o	o	x	x	II.
III.	o	x	o	x	III.
IV.	o	o	o	o	IV.
	I.	II.	III.	IV.	

It may be seen that no serum agglutinates the red cells belonging to its own group, but will agglutinate and may hemolyse corpuscles of other groups, except Group IV. By having on hand serum of Group II. and III., the agglutinating and classifying tests are easily made, not requiring over fifteen minutes.

We have made it a practice of having at our command suitable professional donors, properly classified through physical examinations, and with negative Wassermanns. They can all be reached by telephone, and are paid a fee for their blood.

By having this group of professional donors, the time of making the tests is greatly lessened, and only need of classifying recipient or patient. In emergency, a Group IV. donor can be used to transfuse any other class.
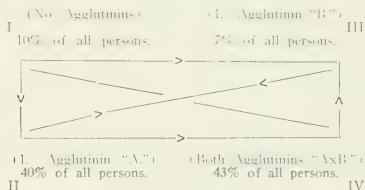
MOSS AGGLUTINATION GROUPS.

Essential for safety; serum of recipient should not agglutinate corpuscles of donor.

If you do not have professional donors suitably classified, it is always best to use the nearest blood relative.

The second danger lies in transfusing an excessive amount of blood. This may lead to embarrassment of circulation, dilatation of the heart and and pulmonary oedema. The question of dosage is an important one and depends upon several factors; age of individual, condition for which transfusion is indicated, and conditions of the circulatory apparatus, especially the myocardium. In any form of myocardial derangement, if transfusion is indicated, small amounts should be given, and repeated at definite intervals, to avoid myocardial embarrassment.

Generally speaking, 500 to 1000 cc. is the usual amount transfused, except in the blood diseases, in which 250 to 350 cc. seems to suffice to stimulate the blood-forming organs.

Infants under six months of age receive 60 to 90 cc., given into the longitudinal sinus or jugular vein.

Danger from emboli can be avoided by proper technique. In using citrate blood, we pass the blood through several layers of gauze.

REACTIONS.

The Mayo clinic reports 20 per cent. of transfused patients to have some degree of reaction. The Crile clinic does not report any reactions, believing them to be due to improper grouping. Our reactions have only been two in our series, and both were due to faulty grouping.

The ease and simplicity of the citrate method of transfusion will suggest an increasing number of indications for its use. Who knows, but what some of the acute infections may be treated by transfusions of small therapeutic doses of blood from donors immunized by the disease, or by vaccination.

The future alone will solve these questions. As stated by one of the investigators, the subject of blood transfusions has thrilled the imagination of man, ever since the discovery of the circulation of the blood. In the last quarter of a century some of these dreams have been realized. The difficulties of technique of the old methods; the uncertainty of success; the pain, infection and life-long scars to patient and donors; the impericisms of its therapeutics relegated its use to the court of last resort.

The newer method of blood transfusion makes possible new applications. They open up a new field of therapeutics, a field that will possibly solve some of the present insoluble enigmas in the treatment of diseases, and in the conservation of human life.

These matters are not capable of animal experimentation, and I cannot do more than suggest these possibilities to the medical men to develop them. The time has arrived when we should seriously begin to study blood dosage and therapy.

CONCLUSION.

1. Salt solution will never raise a blood pressure the second time. Transfusion of blood alone will save the patient.

2. The Citrate Method is the method of choice, because of the ease of application and preservation of important blood vessels for future transfusions, or other intravenous therapy, should occasion require.

3. Transfusion is a specific for haemorrhage of the new-born. In haemorrhagic diseases it will replace blood loss, stop the haemorrhage, but not cure the condition.

4. Transfusion saves delay and decreases mortality in cases with secondary anaemia requiring operation, as fibroid tumors and jaundice.

5. Transfusion of blood opens a new field of therapy in the treatment of chronic infections.

6. Most reactions can be averted by making correct group tests, and transfusing from the same group, except in extreme emergencies, when Group IV. may be used without grouping. In a series of one hundred cases, our reactions have been 6 per cent., and 4 per cent. due to mistakes in grouping.

DISCUSSION.

DR. LUTHER P. HOWELL, Columbus: I wish to mention the facility with which transfusion can be done in infants before closure of the anterior fontanelle. As you recall the superior longitudinal sinus anteriorly is located directly in the median line although at the posterior fontanelle it lies to the right. If the needle be introduced just anterior to the posterior angle of the anterior fontanelle and directed backward at an angle of 45 degrees with the interparietal suture to a depth of about one-sixteenth of an inch, the point of the needle will not impinge upon or injure the walls of the sinus, as it lies near the center of the lumen. The precaution must be made to keep the hand supporting the needle tightly steadied against the head and to inject the blood relatively slowly. Furthermore, in haemorrhage disease of the new-born it is necessary to type the blood, if that of the father be given and the use of only a small amount is necessary.

1. Dennis, J. B.: Philos. Transact., June 25, 1667.
2. Cole, G. W.: Proc. Soc. Exper. Biol. and Med., Vol. IV., p. 6-8 Haemorrhage and Transfusion. N. Y., 1909.
3. Lindman, E.: Amer. Jour. Dis. Child, 1913, Vol. VI., p. 28-32.
4. Kimpton, A. R., and Brown, J. H.: Jour. A. M. A., 1913, Vol. IXI, p. 117.
5. Unger, L.: Journal A. M. A., 1915, Vol. IXIV., p. 582.
6. Lewishon, R.: Medical Record, Jan. 23, 1915.
7. Blood Transfusion, Haemorrhage and the Anemias. Bernheim, J. P., Lippincott, 1917.
8. Lindeman, E.: Journal A. M. A., 1919.
9. Unger, L.: Journal A. M. A., August, 1919.
10. Landois, I.: Die Transfusion des Blutes, Berlin, 1911.
11. Moss, W. L.: Johns Hopkins Hosp. Bull., 1910, Vol. XXI., p. 3 73.
12. Pemberton, J. D., Mayo Clinic, Vol., 1918.

OBSERVATIONS UPON SCARLET FEVER, DIPHTHERIA, AND MEASLES AT THE CINCINNATI CONTAGIOUS HOSPITAL.*

By Albert J. Bell, A. B., M. D.,

Visiting Staff, Contagious Group, Cincinnati Hospital.

Although there are numbers of good men who, patiently and perseveringly, are working in their laboratories and wards upon the problems which our contagious diseases present, and the results of their efforts appear at intervals, one is impressed with the comparatively little written upon the subject. I refer in this paper only to scarlet fever, diphtheria, and measles. This may be due to a placid conclusion on the part of many that our text-books have settled the clinical signs and symptoms and that repeated failures along etiological and bacteriological lines yield little of promise for the future. This I think is incorrect and someone's persistent efforts will eventually be crowned with success.

Scarlet fever appears variously disguised, probably more so than any other contagious disease, and if we can find out practically for ourselves that we have in the past laid too much stress upon certain so-called classical signs and not enough upon others and that a rearrangement of some of our ideas seems advisable, we may be helped to an earlier recognition and, therefore, a more prompt isolation and treatment of this affection. During the last year in the contagious hospital we have had an excellent opportunity for studying this disease especially, and it is my desire to furnish statistics as we found them in this and the other diseases, with certain observations which were made concerning clinical manifestations, laboratory findings, and treatment.

Observations were made upon over 300 cases of scarlet fever. The following summary indicates in percentage form our findings in the so-called classical symptoms and diagnostic signs:

Scarlet fever, 315 cases. Onset with vomiting, 50 per cent.; onset with headache, 4 per cent.; onset with sore throat, 65 per cent.; eruption, whole body, 46 per cent.; eruption, partial, 35 per cent.; mouth pallor, 57 per cent.; rash on soft palate, 38.6 per cent.; membrane on tonsils, 29 per cent.; papillæ enlarged, 56 per cent.; glazed tongue, 17.7 per cent.; anterior cervical glands enlarged, 95 per cent.; submaxillary glands enlarged, 72 per cent.; eruption gone from body, five and one-half days; desquamation began in six and three-quarter days; blood count, leukocytes average, 17,000; polymorphonuclears, average, 78 per cent.; large lymphocytes, average, 6.3 per cent.; small lymphocytes, average, 10.1 per cent.; eosinophiles, average, 2 per cent.; albumin, 11 per cent.; granular casts, 4 per cent.; hyaline casts, 2.5 per cent.; blood cells, 4 per cent.; myocarditis, 6 per cent.; irregular heart, 3 per cent.; murmurs, 8 per cent.; mastoiditis (no facial palsy in this series), 1 per cent.; arthralgia (all cases had immunizing doses of diph-

theria antitoxin), 6 per cent.; acetone, 49.5 per cent.; diacetic acid, 22.6 per cent.; indican, 73 per cent.; temperature gone in five and two-third days; nephritis, 2 per cent. The average white count of cases which died was 17,262. Preponderance of the staphylococcus may have influenced all leukocyte counts.

Concerning the above summary a few comments seem pertinent: Onset with vomiting occurred in only 50 per cent. of our cases, which is rather disappointing, as so much stress has always been laid upon this sign. McCullom[1] says that it occurred in 80 per cent. of his cases, but Welsh and Schamberg give their figures also as 50 per cent., and add that they consider this rather lower than usual. I think that this is a just criticism and that in most epidemics the figures would be considerably higher.

We observed mouth pallor in 57 per cent., which is also lower than we would expect. No statistics were obtainable from other sources in regard to this, McCullom merely says that it occurs constantly in moderately severe cases. It has been our experience that the rash occurs on the face in only a small number of the cases, but when this is present or if there is only a febrile blush upon the cheeks, the skin around the mouth and nose remains exempt. When this is seen I believe it to be quite characteristic.

Thirty-eight and six-tenths per cent. had rashes upon the soft palate and fauces and where this is present, namely, a generalized blush, punctate in character, I believe it to be our most important diagnostic sign.

The papillæ appeared enlarged in 56 per cent. of our cases. Concerning this McCullom says that the condition is constant, but may be missed at times, and Welch and Schamberg say that it may or may not be present in mild cases. When present, even with the glazed tongue (17.7 per cent.), it is not absolutely pathognomonic, as it may occur in certain forms of gastro-intestinal disturbance in which there is not the slightest suspicion of scarlet fever. The strawberry tongue, however, taken together with a generalized blush, punctate in character, upon the soft palate and fauces, need leave very little doubt as to the character of the disease.

I think these two symptoms are very much more significant than an apparently characteristic rash upon the body. We have tried to emphasize the importance of laying more stress upon the mouth symptoms and not depending upon the body rash. However, the whole picture should be considered

Our average white count was 17,000. The maximum was 38,000. The text-books lead us to expect a uniformly higher count than this. We felt that a satisfactory one was between 20,000 and 35,000. Kotschetkoff and Bowi's[2] figures are between 10,000 and 40,000, Reider's 40,000, Felsenthal between 18,000 and 30,000, and Tileston between 18,000 and 40,000.

The average polymorphonuclear count was 78 per cent. Kotschetkoff gives between 85 and 98 per cent.

1. Osler's Modern Medicine.
2. Quoted by Welch and Schamberg.

The low percentage of eosinophiles, 2 per cent., was probably due to the fact that the blood counts were made early in the disease.

McCullom observed albumin in 72 per cent. of his cases at the South Department, while Roger reports 38 per cent. Our cases showed the presence of albumin in only 11 per cent. I believe that a practical reason for this may be found in our routine treatment. All cases were confined to bed for at least three weeks and kept upon a strictly milk diet until their temperatures were normal for seven days. Eggs and broths were withheld until the fifth week and red meats until the latter part of the sixth. Of equal importance with this is the systematic giving of large quantities of water from the time of their admission to the hospital. At first potassium citrate was ordered, more or less as a placebo, to be given hourly or two hourly in water, with the idea that the patients would get the fluid more religiously if medicine were ordered with it. How much restraining influence the alkalinizing power of this drug exerted upon the presence or absence of albumin in the urine we will consider later.

In our estimate of nephritis we included all cases showing the presence of albumin, casts, and red blood cells, and this we found to be only 2 per cent. Welch and Schamberg[3] quote Vogl as reporting 34 per cent. of nephritis in his cases; Cadet de Gassicourt, 30 per cent.; Baginsky, 9.57 per cent.; Caiger, 3.32 per cent., and Holt gives as his figures between 6 and 10 per cent.

Let me call attention to the fact that about 50 per cent. showed the presence of acetone in the urine; less than half that number showed diacetic acid, and almost 75 per cent. reacted for indican.

Practically all the cases desquamated, although some very slightly.

None of our scarlet fever cases contracted diphtheria in the house, although two or three showed the presence of the Klebs-Loeffler bacillus upon admission. The most susceptible period for this disease is the third, fourth and fifth week. Variat and Deve report 30 cases positive for the Klebs-Loeffler bacillus in 525 scarlet fever patients; Garret and Washburn,[4] London Fever Hospital, report 1 per cent.; Welsh and Schamberg,[5] Municipal Hospital in Philadelphia found between 19 and 32 per cent. positive. Some allowance should be made for the method employed in reporting the presence or absence of the Klebs-Loeffler. We used the Westbrook classification entirely, which is liberal and will be referred to under diphtheria. At least four cultures were taken from the noses and throats of all scarlet fever patients.

The so-called Pastias sign in this disease, namely, the accentuation of the rash in the normal folds, especially on the anterior surface of the elbow, has not been noticed except in a few instances, so that no significance has been attached to it.

3. Ibid
4. Quoted by Welch and Schamberg
5. Ibid

Of like importance is the Rumpel-Leeds phenomenon or the hemorrhages at the elbow from compression of the upper arm by means of a bandage. Observations made by others have shown it to occur with equal frequency in measles and in normal children.

In taking up the treatment of special conditions we may first refer briefly to the subject of immunization against scarlet fever. We have had practically no personal experience with this line of work, except to give one light case which was exposed to the most virulent form of the disease one million killed streptococci taken from scarlet fever patients (a vaccine which was on the market) and which case continued to have a mild attack, and another, a very malignant case, five daily doses from 500,000 to 4,000,000 of the same scarlet fever vaccine. This patient's condition was uninfluenced by the treatment and the patient died in a few days. The above should come under the heading of treatment of the disease rather than immunization. If there is any close connection between the streptococcus and the virus of scarlet fever we would look for our best results from an antistreptococcus serum, made from scarlet fever patients rather than a vaccine, as the former (the serum) already contains the antibodies and should act more promptly, while the latter (the vaccine) simply helps the patients to form his own. The field for the vaccine is in immunization.

With the use of the ordinary antistreptococcic serum made up of streptococci not from scarlet fever patients we have noticed little benefit even in doses of 80 or 90 cc. in twenty-four or thirty-six hours. If it is used at all it should be made from the streptococci from blood, throat, or glands of scarlet fever cases. Such a serum has been hard for us to obtain from any source, because of the difficulty we have experienced in isolating streptococci from our cases.

Federinski in Moscow (1910), in an analysis of 317 cases which received the antistreptococcic serum (made from scarlet fever streptococci), says that it helps chances of recovery if given before the fifth day. His dosage was 200 cc. to adults and 100 to 150 cc. to children, repeated in twenty-four or forty-eight hours if necessary. Mathias Nicoll, New York (1910), reports only fair results. If obtainable, it should be used in some cases, in enormous doses always, for lack of something better, either subcutaneously or intravenously, according to immediate needs. It might help minimize the complications

Professor Schwenkenbecker, director of the Frankfurt Hospital Medical Clinic, recommends the injection intravenously, not later than the fourth day, of serum (healthy as to syphilis or tuberculosis and culturally sterile), taken from at least three (namely, a polyvalent serum) scarlet fever cases suffering from a severe but uncomplicated type of the disease in late convalescense. Treatment with this sera should cease not later than the eighteenth to the twenty-fourth day from the onset. The dose should be 40 cc. for children and 100 cc. for adults, and doses may be given at intervals of from

one to seven days according to the severity of the case. He suggests that only the severe and unquestioned cases of scarlet fever be injected.

Karl K. Koessler and Jessie M. Koessler,[6] in experiments concerning specific antibodies in scarlet fever, concluded that "the serum of scarlet fever patients contains specific antibodies for an unknown virus which seems to be present especially in the cervical lymph glands." Personally, I think that we should direct out efforts toward discovering a specific serum for the treatment of this disease to the preparation of sera derived from the blood stream or, more probably, from the cervical lymph glands of scarlet fever patients, rather than to vaccines or serums containing the streptococcus or its antibodies.

Out of 50 or more nurses who have been on duty in the wards, three (about 6 per cent.) contracted the disease in the house, while none of the internes did.

W. H. Waters, of Boston, reports results in immunization against scarlet fever, of nurses on contagious duty. He used different strains of streptococci, killed and standardized in usual way, taken from throats of scarlet fever patients. For two or three weeks before going on duty the nurses received three immunizing doses, of 50,000,000, 100,000,000 and 200,000,000 organisms of a polyvalent vaccine. Of those receiving the vaccine 2.7 per cent. contracted the disease and of those not receiving it 35.7 per cent. contracted it. These figures are rather amazing as his nurses must have been unusually susceptible.

Kolmer of Philadelphia, in trying to raise the streptococco-opsonic index, found experimentally that he was able to do so slightly, but concluded that it was so slight as to make the likelihood of establishing an immunity against streptococcic infection very dubious. Again, in experimental studies on streptococcus antibodies with special reference to complement fixation reactions, he concludes that a streptococcus produces a specific antibody up to a certain limit, but "finding but 11.2 per cent. of positive reactions in scarlet fever tends to show that streptococcus infection in scarlet fever severe enough to produce immune bodies is not so common as is generally believed."

Nasal and ear discharges were reported promptly and a number of autogenous and stock vaccines (in all ten, an inconclusive number it is true) were prepared.

It is the opinion of most workers that stock vaccines give equally as good, if not better results than the autogenous, because the former can be administered much more promptly and several days are gained for the patient, a very important consideration. Our results with these vaccines were not brilliant. Cases using vaccines had no local treatment. Irrigations were employed for the others. Except in one or two instances we could not see that the discharge was in any way modified by the vaccine and on the whole, those having local treatments ran a shorter course. The dosage in

each case was started with about 200,000 and each succeeding dose was doubled at intervals of from two to ten days, according to indications. This was carried up to 128,000,000 in some cases. This method has so far been disappointing, but in the hands of Kolmer, of Philadelphia, good results have been reported. It is possible that in some instances our intervals of administration and dosage were faulty, yet the method is certainly in line with modern vaccine therapy in other directions. Many cases, however, having local treatments, where intelligently applied, yield results, which, if vaccines were being used, would be considered brilliant.

We have taken the opportunity in our wards of applying wherever feasible, the treatment for nephritis as suggested by Dr. Martin Henry Fischer.[7]

This therapy is based upon certain theories, or more correctly, facts, since they have been confirmed by laboratory experiments and as they are a departure from our formerly accepted views on nephritis, it may be well to briefly summarize a few details of his work and conclusions for the benefit of those who are not familiar with them. They are as follows:

It is assumed that nephritis is due to an acidosis in the kidney. Emphasis is laid upon the colloidal structure of the blood, both red and white corpuscles and the liquid portion, also that the urinary membrane, namely, everything between the urine and the blood, consists of various emulsion colloids in the solid state. Colloid material is also present in the urine normally, but is not visible as albumin in our ordinary tests.

The fluids and tissues of the body (except the gastric juice, urine, sweat, vaginal secretion, and alimentary contents, when fat is fed) are practically neutral in reaction. Normal blood is neutral in reaction, but contains both alkalies and acids.

An abnormal production or accumulation of acid in the kidney renders the colloidal urinary membrane soluble and permits a part of it to pass into the urine as albumin.

This has been demonstrated by experiments. Fibrin, an albuminous structure, when mixed and shaken with plain water (of neutral reaction) swells only slightly and the water shows no reaction for albumin. If hydrochloric acid is added there is greater swelling of the fibrin and albumin is present (by the precipitation of the fibrin) in the water in accordance with the amount of swelling. If sodium chloride or any other salt is mixed with the hydrochloric acid, less albumin goes into solution, the higher the concentration of the salt. Gelatin (another colloid) acts practically the same way as fibrin.

A high alkali content can as readily put the colloids, fibrin, and gelatin into solution (namely, dissolve the albumin) as can an acid. This is probably no factor in the production of a nephritis as the normal CO_2 production in the living cells tends quickly to neutralize it.

Fischer found that by injecting acid into the ear of a rabbit, its nor-

mally alkalin urine became acid. Albumin, casts, epithelial cells, blood corpuscles, and hemoglobin appeared promptly in the urine which was also diminished in quantity. Edema of the tissues was noticed as well.

An over supply of acid in the tissues in extreme muscular exertion and the severe anemias, without adequate oxidation, shows albumin in the urine.

Contrary to the views of many, he holds that albuminuria is the constant accompaniment of salt starvation.

Actual experiments on the kidney by Fischer are in line with the preceding observations. He found that the structures of the kidney in the presence of an acid swell, take in water, and part of the colloid material is dissolved as albumin and precipitated as granules.

This brief summary suggests the "Fischer" treatment for nephritis, namely, an alkali, salt, and plenty of water.

It occurred to us that as the contagious diseases are frequently accompanied by an acidosis, as exemplified by the presence of acetone in about 50 per cent. of our cases and diacetic acid in 22.6 per cent., that the alkaline treatment might help to control the progress in the severe septic types of the disease. Apparently it exerted little or no influence in staying the course of the purely septic types which were unaccompanied by any special nephritis. Fischer says that he would not expect it to have any material influence upon that type of case. Sodium carbonate given by the mouth was not well tolerated as a rule, and seemed to be somewhat more irritating to the rectum than a normal salt solution. However, a large majority of the cases retained a sufficient amount in that way. Potassium citrate was substituted when giving an alkali by mouth and has been given to all my cases hourly or two hourly, whether or not they had evidences of albumin or nephritis. Probably the low percentage of albuminurias (11 per cent.) and that of nephritis (2 per cent. in 388 cases of scarlet fever) observed in our wards is due to the routine alkaline "plenty of water" treatment, which all the cases have had. Their urine part of the time was alkaline and never highly acid.

Two cases present interesting features:

CASE I.—M. D., male, aged three years. Severe septic type with both ears discharging, profuse nasal discharge, enlarged glands, weak, irregular heart with bruit at apex, eyelids, and feet edematous. Urinalysis, albumin negative. Amount of urine very scanty, blood cells and hyaline casts. Started alkaline-salt solution per rectum. The solution contained sodium carbonate (crystals) 10, sodium chloride 10, in 1000 cc. of water. A half strength dilution of the above was used. Four ounces were given per rectum every three hours and were expelled occasionally. Potassium citrate, grains five in water, was given by mouth every one to three hours.

On the ninth day of the illness Fischer's solution was given intravenously. Same formula as above was used except that sodium chloride was increased to 14 in the 1000 cc. of water and a half dilution given. Only 10 ounces were used as the patient showed signs of collapse. At least a pint

and a half should have been given very slowly had we been able to do so. Next day one pint was given again intravenously. The amount of urine passed increased promptly, and the edema disappeared. Gradual improvement of general symptoms with complete recovery resulted.

CASE II.—J. D., male, aged four years. Light case of scarlet fever with temperature reaching normal on the fifth day. He passed from 8 to 33 ounces of urine daily up to the thirty-first day of the illness. On the twenty-seventh day (end of fourth week) the urinalysis showed: Specific gravity, 1010; albumin, a heavy trace; few coarse granular casts; red and white blood cells.

The child was somnolent and was aroused with difficulty. Vomited several times. Pulse varied between 90 and 122, with blood pressure high (systolic pressure sometimes reaching 144). The child seemed on the verge of uremic convulsions. There was puffiness of the face and eyelids and slight edema of the feet. There was no fluid in the serous cavities at any stage.

For thirteen days after the nephritis commenced, except once, albumin from a slight to a heavy trace was reported daily in twenty-four hour specimens. It then disappeared not to return again.

During the presence of albumin, red and white cells were found in abundance. Casts were rare. An occasional granular, and a few blood casts were reported once and part of one cast another time. There were no hyaline casts. After eight days the blood cells were few in number and gradually disappeared, to be entirely gone about the eighteenth day. The specific gravity varied between 1002 and 1028, usually between 1002 and 1010. The urine was reported as acid only twice after the fourth day. The amount of urine passed daily varied from 30 to 60 ounces.

TREATMENT. The treatment was as follows: For ten days after albumin was discovered the patient had sodium chloride, grains five, and potassium citrate, grains eight, by mouth in as much water as he would take every hour, day and night. Fischer's solution, one-half dilution (of the sodium chloride 10, sodium carbonate, crystals 10, water 1000 cc. strength), ounces five, per rectum was given at two-hour intervals during the day and three-hour intervals during night, and was retained. After ten days the intervals of administration both by mouth and rectum were lengthened.

During the period of high blood pressure, veratrum viridi, minims two, every three hours, was given during the day. Fischer's solution intravenously was not necessary.

Blaud's pills were started during convalescence as a tonic. During the attack the child showed a mild grade of anemia. The red blood cells were 4,600,000. Recovery was complete.

There were several interesting features about this case. He started with what appeared to be a terrific case of nephritis with the urine absolutely loaded with red blood cells and a large amount of albumin. One striking

thing was the great scarcity of casts of all descriptions. How much this was influenced by keeping the urine absolutely alkaline, by the constant administration of salt, and the ingestion of large quantities of water, is an interesting question. With the starting of the treatment all symptoms improved and continued to do so consistently.

We found that grains twelve to thirteen hourly of potassium citrate by mouth in the adult and grains five to seven in children, aged four to seven years, was sufficient to keep the urine alkaline.

As I have said before, nephritis has been of rather rare occurrence in our wards, but whenever tried the alkaline salt treatment has given satisfactory results.

True relapses or reinfections were not observed, but delayed rashes occurred in one or two instances.

Eighteen blood cultures were made during the year from scarlet fever patients. Of these nine were negative. In the other nine cases the staphylococcus pyogenes aureus was recovered seven times and the albus twice. We were unable to recover the streptococcus from the blood.

The throat and nose cultures almost uniformly showed the presence of staphylococci, occasionally mixed with a few streptococci.

Atmospheric plate cultures (88 in number) in wards before fumigation showed the presence of the staphylococcus aureus and albus, the streptococcus pyogenes, but never the Klebs-Loeffler bacillus. After fumigation with formaldehyde, plate cultures were always negative.

Twelve cervical glands of scarlet fever patients were aspirated with aseptic precautions in an effort to corroborate the claims of Vipond made in the spring of 1911, that he had found the specific organism of scarlet fever in the glands of patients suffering from this disease. The cultures were sterile in nine cases; the staphylococcus pyogenes aureus was isolated twice and the pyocyaneus once. Our results did not verify his findings. This has also been the experience of others. Experiments by Dr. Nicoll show that Vipond's bacillus was probably a contamination from the asbestos packing of his syringe.

The following summary shows observations made upon 76 cases of diphtheria:

Onset with sore throat, 84 per cent.; onset with vomiting, 33 per cent.; membrane on tonsils, 85 per cent.; membrane on soft palate, 36 per cent.; inflammatory swelling, 30 per cent.; membrane gone on the average in two and seven-elevenths days; temperature normal on the average in three and three-quarter days; erythema (not from serum), 5 per cent.; urticaria (not from serum), 14 per cent.; otitis, 5 per cent.; albumin, 12 per cent.; adenitis, 47 per cent.; paralysis, soft palate, 5 per cent.; paralysis of other muscles, 4 per cent.; myocarditis, 16 per cent.; endocarditis, 28 per cent.; slow pulse, 4 per cent.; arthralgia, 2.6 per cent.; acetone, 28.5 per cent.; diacetic acid, 14 per cent.; indican, 32 per cent.; serum rashes, 16 per cent.; antitoxin,

average dose, 40,000 units; highest dose, 355,000 units; blood count: Leukocytes, average, 13,633.

Types of Klebs Loeffler bacilli found in Wesbrook classification: C, 58 per cent.; D, 39 per cent.; A, 22 per cent.; E, 8 per cent.; E_2 and F_2, 5 per cent.; B, D_2, and F_1, 3 per cent. Other solid forms occurred less frequently.

Glancing at the table we see that vomiting occurred at the onset in only 18 per cent. of the cases, while in scarlet fever the percentage was 50.

A striking feature about the table is that the average dose of antitoxin was 40,000 units. This is accounted for by the fact that a number of desperate cases, having been sick about a week before admission, required enormous doses which brought up the average considerably. Many required only small doses. Our rule was to give from 2000 or 3000 to 12,000 units from two to three times in twenty-four hours, until signs of improvement were noticed.

A husband and wife, sick one week before admission, came in completely overwhelmed by the disease. The former had the pharyngeal type, his pharynx being completely covered by a membrane about one-eighth of an inch thick. He had the record dose, 355,000 units. He developed some arrhythmia, but showed no serum rashes or arthralgia. He was in an advanced stage of tuberculosis before acquiring diphtheria and died from that disease later. His wife had a bad laryngeal type of diphtheria, with pronounced stenosis, loss of voice, and extreme prostration. She received 345,000 units and made a complete recovery, without serum rashes, arthralgia, evidences of myocarditis, or any other complication. Advanced laryngeal cases received antitoxin unsparingly.

Whether or not hospital cases receive more antitoxin than is absolutely necessary, they, at least, cannot be judged by the standard set in private practice where the cases receive treatment promptly.

Our cases show some features which are worth mentioning. The average time for the disappearance of the membrane was two and two-third days and normal temperature averaged three and three-fourth days. Paralysis of the soft palate occurred in only 5 per cent. Other paralysis, 4 per cent. Arthralgia was noticed in only 2.6 per cent. and serum rashes in 16 per cent. Concentrated serum was always used. No anaphylactic phenomena were observed in any of our cases. Our mortality for diphtheria as reported up to January 1, 1912, was 3⅓ per cent., while for scarlet fever it was 6.5 per cent. This is at least an illustration of the principle that large doses of antitoxin need not be feared, and that it neutralizes all the toxin. The converse applies forcibly to insufficient dosage. Promptness in administration is an important guide to the size of the dose.

The Wesbrook[a] classification was used routinely in examinations for the Klebs-Loeffler bacillus. A, C, and D, the granular types, were regarded

as positive and when found three successive negative cultures were required before discharge.

A_1, A_2, B, B_2, C, C_2, and E (the barred types except E), were called doubtful, and when found put the patient back for only one culture instead of three. The solid forms were regarded as negligible. This method is a liberal one, as it makes a distinction between the virulent and non-virulent types.

No use was made of the Diazo reaction in diphtheria as a differential sign between a purely serum rash and true scarlet or measles. It occurs in 17 per cent. of scarlet fever cases, 12 per cent. of diphtheria, and 75 per cent. of measle cases. In the latter it might be helpful.

Little difficulty was experienced with the persistence of the Klebs-Loeffler bacillus in the throats of convalescing individuals. This happened only two or three times. The early negative findings were undoubtedly influenced by frequent throat irrigations and sometimes nasal, of normal salt solution or bichloride solution (1 to 12,000) or simple applicatons of the latter (1 to 4000).

L. M. DeWitt and others recommend the application and sprays of fresh cultures in broth of the staphylococcus pyogenes aureus for persistent Klebs-Loeffler bacilli in the throat. This should not be done until convalescence, when the mucous membrane presents a normal healed surface. There is no incompatibility between the Klebs-Loeffler and the staphylococcus, but the latter assists in reinforcing the normal throat flora.

Max Crohn[9] recommends small doses of antitoxin (2000 units) subcutaneously for post-diphtheritic paralysis and reports good results. We have not tried it, and should hesitate to do so except in very favorable cases for fear of serum sickness.

Bingel[10] recommends intraspinal injections of diphtheria antitoxin for late cardiac failure after this disease. The condition is so grave that anything which gives even remote promise should be tried.

Cumberlage, of England, recommended the use of antitoxin by the mouth. The initial dose was 4000 units, followed up if necessary by 2000 units more. He did not observe serum rashes or joint pains following the use of this method, and obtained result within a few hours after administration.

We tried this with a few cases (five in number) and selected them with reference to mildness rather than severity of type. It was administered in milk and usually well borne. We used only small doses, but seeing very slow response gave more than he recommended. The average disappearance of nasal discharge was five and one-half days and of membrane on the tonsils seven and one-third days, as opposed to the subcutaneous method, which was two and two-third days.

9. Munch. med. Woch. 1912, lix, 84
10. Deutsch. Arch. f. klin. Med. 1911

With the injection of diphtheria antitoxin intravenously we have had no experience. E. Freedberger and S. Mita[11] claim from their experiments that larger doses may be borne and that there is less chance of an anaphylactic reaction when applied directly to the blood stream and so avoiding a reaction with the body tissues. In very desperate cases it might appeal to us as offering a better chance to more promptly neutralize the toxins.

Acetone was found in our diphtheria patients in only 28.5 per cent., but only one examination was made for each of the cases. F. Reicher,[12] of Hamburg, found it in 65 per cent. of his diphtheria patients during the febrile stage and in 40.2 per cent. of all other anginas and is, therefore, inclined to regard it as of diagnostic significance. I cannot see that it is needed especially as an aid, for either a laboratory or clinical case of diphtheria will have its appropriate treatment. Even in private practice one should not be satisfied with just one negative culture.

Our routine method of staining for the Kelbs-Loeffler bacillus has been done with the standard Loeffler's methylene blue. Very recently we have tried in conjunction with this a stain proposed by Dr. Marie Raskin[13] in a paper read before the Royal Clinical Institute, of St. Petersburg. The solution is composed as follows: 5 cc. of glacial acetic acid, 95 cc. of distilled water, 100 cc. of 95 per cent. alcohol, 4 cc. of an old and long-standing methylene blue solution, 4 cc. of Ziehl's carbol fuschin.

The method is to drop the mixture on the prepared slide and then boil over a flame for eight to ten seconds. After five seconds the slide is washed in water, dried, and examined. The polar bodies appear as deep blue, while the rod is a bright red.

Practically, our stains so far show the rods to be a pinkish color, while the granules stand out very well as dark bodies. Other rods and cocci likewise take the pink stain. From our limited experience in its use, it appears to be a good stain and I think that the polar bodies stand out more prominently than with the methylene blue method alone.

Before closing let me mention a few observations concerning measles and rubella. Our average white count for all ages in both was between 7000 and 8000, somewhat higher than we would expect. All had an increased polymorphonuclear count.

The cervical and submaxillary glands were enlarged in practically all of our rubella cases, but in none markedly so. The submetal gland was enlarged in a few cases (recent cases show their presence more often), the post-auricular were enlarged more frequently. In rubella the rash was of the maculo-papular type in 81 per cent.; of the erythematous type in 19 per cent.

In measles, acetone and diacetic acid (each) were present in 22 per cent which is, I believe, lower than usual. Indican occurred in 88 per cent.

11. Deutsch. med. Woch., February, 1911.
12. Munch. med. Woch., October, 1911.
13. Deutsch. med. Woch., December, 1911.

In rubella both acetone and diacetic acid were negative in all cases, a fact which may be found to have some diagnostic significance; indican was positive in 50 per cent.

REPORT OF NINETEEN CASES OF HYPERPLASIA OF THE THYMUS GLAND, TREATED BY THE X-RAYS.*

By JULIEN E. BENJAMIN, M. D., AND SIDNEY LANGE, M. D.

Cincinnati.

HISTORICAL.

In 1855 Kapp called attention to instances of sudden deaths in childhood following cyanosis and stridor, in which at autopsy nothing abnormal except an hyperplastic thymus could be found. Since that time clinicians have paid much attention to thymic hyperplasia and faulty involution thereof. The studies of A. Paltauf[1] in 1889 established the frequent combination of hyperplasia of the thymus with status lymphaticus and aplasia of the cardio-vascular system. It was he who called attention to the necessity of considering causes other than mechanical in the sudden deaths among such patients. He spoke of a disturbance connected with a "lymphatico-chlorotic constitution."

For a long time it was thought that an abnormally large thymus was always accompanied by a status lymphaticus, but it is now definitely known that a status thymicus can occur independently of a status lymphaticus. This has been proven from both laboratory and clinical standpoints. For instance, Weisel and Hedinger[2] have shown that hyperplasia of the chromaffin system and status lymphaticus go hand in hand, while in pure hypertrophy of the thymus this is not true.

The cases which are recorded in this paper represent a larger number of cases of true thymic hyperplasia than have heretofore been reported. In no case were there symptoms of status lymphaticus. Thymic hypertrophy thus became a distinct entity with as yet no cure.

In 1896 Rehn reported 5 cases of thymectomy for the relief of tracheal obstruction. Shortly before this thymopexy was employed, but was a complete failure, except for temporary relief of stenosis. Thymectomy was resorted to entirely in these cases until 1903, the mortality associated with this operation being about 11 per cent. In this year Heinecke[3] showed that X-rays have a profound influence on lymphoid tissue in the guinea pig, especially on the thymus gland. With this discovery a very valuable chapter was added to medicine, for it was not long before it was shown that by the immediate and intensive application of X-rays, the most hopeless case could be saved; also, that all the symptoms resulting from an enlarged thymus could be permanently cured by subsequent dosage. The first case thus treated was reported by Dr. Alfred Friedlander.[4] Led by the work of Heinecke, Dr. Friedlander and Dr. Sidney Lange first worked with guinea pigs, noting the effect of frequently repeated exposures on the lymphoid tissues. Not long after this a case of acute tracheal stenosis on the basis

of thymic hypertrophy was relieved and permanently cured by the application of the X-rays. At this early date one difficulty existed. Radiography was far from its present stage of perfection and it was almost impossible to obtain clear pictures of the thymic region. Furthermore, there was no real accurate method of measuring dosage. It is because of the passing of these difficulties that the present report and results are possible.

This study comprises one year's observation on all kinds of cases coming under our supervision at the Children's Department of the University of Cincinnati (Ohio-Miami Medical College) Clinic. A total of 225 cases were seen in that time, of which 19 showed undisputed evidence of enlarged thymus, or 8.47 per cent.

The diagnosis of an enlarged thymus is usually simple. The chief complaint is nearly always, coughs or attacks of choking which come and go, appearing frequently in paroxysms. One point of interest is the fact that the mothers usually explain that the child does not show the prodromal symptoms of a cold, but while apparently well, begins to cough during the night. This is repeated for several nights and then disappears, to return in a similar manner in a very short while. Only on further cross examination is the information elicited that there is noted occasional cyanosis or tendency to choke or stridor. Most of the cases were very well developed and nourished. The lymphatic glands, other than the posterior cervical glands showed no hypertrophy as a rule. The spleen was found enlarged in only two cases. The lungs were, as a rule, peculiarly free of râles.

In outlining the gland the following method, spoken of by Sylvester[5] and others as "Threshold Method of Percussion" was always employed: The child is placed on the mother's lap on his back. Percussion is begun well out in the chest with such light strokes that when the ear is within a few inches of the area under percussion only faintest possible resonance is heard. When sound disappears, dullness begins. Some observers outline the borders of dullness by the tactile sense of resistance rather than sound. The outer limits are determined much more easily than the lower boundary. The lower boundary, which may be obtained by auscultatory percussion is relatively less important. The percussion outlines, determined in this way, correspond remarkably close to the roentgenograms. All cases showing enlarged thymus by physical examination or in which there were suggestive symptoms of this condition were submitted for X-ray examination. Treatments were only given to those showing positive X-ray findings.

It is most interesting to note the rapid improvement under roentgenotherapy. Beginning with the first treatment marked progress is usually noted. Shortly after the second treatment the cough has usually abated. With the improvement in symptoms goes a corresponding shrinkage in the size of the gland as shown by subsequent radiograms.

The parents were always cautioned about relapses which occur in a certain number of cases and directed to return for treatment regardless of

appearance of symptoms within six weeks of the last treatment. Three treatments are the usual number given.

In reviewing the clinical literature of the past five years one is struck by the small number of cases reported of this apparently common illness. Furthermore it will be noticed that most of the cases which do come into print have been of the fulminating type. It is altogether likely that the cases coming under this series represent earlier stages of the more severe kinds. In other words, were they to have had intercurrent infections while in the stage of hyperthymetism more urgent symptoms might have been noted. It is probable that the condition was remedied before further symptoms could develop. The condition is important enough to deserve more attention than has been given to it in the past. Early diagnosis and prompt therapy may be the means of eliminating most of the sudden deaths among infants and young children.

Dr. Lange outlines his method of treatment as follows: All of the children who were referred to the X-ray laboratory, were first radiographed to
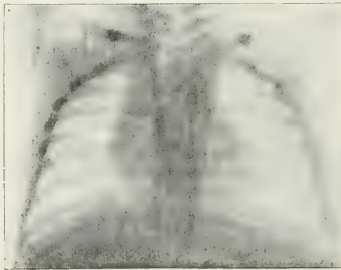
Plate 1. E. G. Age 12 months. October 24, 1916. Child had had frequent attacks of nocturnal cough of a croupy character. Apparently well during the day time. Note broadening at thymic area. This case is typical of the series.

confirm, if possible, the clinical diagnosis. To obtain trustworthy X-ray plates of these cases certain details of technique must be observed. Undoubtedly the difficulty experienced in some laboratories of establishing definite X-ray diagnoses of thymus enlargement has been due to a failure to observe these details of technique. Indeed, in many large clinics the great frequency of enlargement of the thymus glands in young children has been overlooked and in some instances even doubted. While a clinical diagnosis of thymic enlargement is not always difficult, yet it is never absolutely positive without X-ray confirmation. This X-ray confirmation, taken in conjunction with the startling results of X-ray therapy, emphasizes this condi-

tion as a distinct clinical entity and leads to the recognition of many cases which would be otherwise overlooked.

The child to be radiographed must be placed flat upon the back. There must be no tilting to either side. If there is the slightest lateral tilting there is produced upon the X-ray plate an asymmetry of the two halves of the chest and a "flopping" or displacement of the mediastinal and heart shadows to one or the other sides. X-ray plates produced under such conditions are usually valueless, as they cannot be accurately interpreted. It is not always easy to place very young infants symmetrically upon their backs, but repeated trials must be made until a plate is produced which shows the chest areas, that is, the distances from the midline of the spine to axillary borders of the ribs, to be equal on the right and left sides. . Under these conditions, enlargements of the upper mediastinal shadow, whether to the right or to the left of the midline, can be readily recognized. It is essential in the making of these radiographs of very young children that the exposures be almost instantaneous. The reasons are obvious.
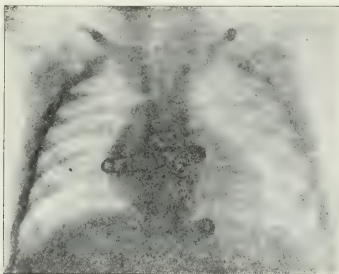
Plate 1-A. Same case as Plate 1. November 7, 1916, after three treatments, with relief of symptoms.

In the series here presented the time of exposure varied from one-sixtieth to one-thirtieth of a second. Even with such short exposures it is not always possible to secure absolutely sharp contours upon the plates. If the time exceeds one-thirtieth of a second there results an amount of blurring of the shadow contours which usually renders the interpretation inaccurate. A very soft X-ray tube should be used on this work, as the delicate thymus tissue will fail to cast a shadow upon the X-ray plate if the quality of the X-ray employed be too hard or penetrating.

As previously stated, the X-ray diagnosis of thymic enlargement is based upon an enlargement (usually a lateral enlargement) of the thymus shadow, which normally rests upon and is continuous with the heart shadow.

Since the breadth of the upper mediastinal shadow varies normally with the age and general condition of the patient and since it may vary from time to time even in the same patient, the X-ray diagnosis is not always easy or free from error. In one case, not included in this series, an apparently normal thymus shadow was obtained when the child was quiet or sleeping, but during a restless crying spell the thymus shadow became greatly enlarged.

The X-ray shadows of congenital heart enlargements are often confused with thymic enlargements. In all cases in which the X-ray diagnosis seemed doubtful an X-ray exposure was given as a therapeutic test, and this test has proven very reliable. It must be conceded, in this connection, that many symptomless and apparently healthy children may show an apparently enlarged thymus upon the X-ray plate and this fact has been illogically cited as evidence against the accuracy of the X-ray diagnosis and the value of X-ray treatment of thymic enlargements. An enlarged thymus in an apparently healthy child may be abnormal although its ill effects may not be manifest until some added strain be put upon the heart or respiratory organs or until the resisting powers of the child be called upon to overcome an acute infection. Post-morten evidence is not always conclusive in these cases as a thymus enlarged *intra vitam* may collapse after the circulation is abolished, although such post-mortem findings have been cited as indicating inaccuracy in X-ray interpretation.

The X-ray therapy was carried out in this series of cases as follows: A Coolidge tube backing up a $9\frac{1}{2}$-inch spark was employed. The rays were filtered through four millimeters of aluminum and a piece of thick leather. The target skin distance was approximately 9 inches. The routine exposure was 25 milliamperéminutes. In mild cases a single dose given over the anterior surface of the chest proved sufficient. In more urgent cases 50 milliamperéminutes were administered at the first treatment, 25 anteriorly and 25 posteriorly. During the treatment the child was kept quiet by four sandbags, one placed across each arm and one across each leg. The interval between treatments was usually one week unless the urgency of the symptoms suggested more frequent applications. The treatments have proven entirely harmless to young children, and if the symptoms are very urgent a second dose may be given within a day or two after the first. In order to get results it is essential that the treatments be comparatively heavy and that they be repeated at sufficiently short intervals. The failure to administer full doses and to repeat them promptly has in very urgent cases led to fatalities under X-ray treatment. Such a distressing occurrence is fortunately uncommon, but when it does happen it casts a doubt upon the diagnosis or upon the efficiency of the X-ray therapy. To guard against sudden deaths before the full destructive effect of the X-ray upon the thymus gland has been elicited, all cases with urgent symptoms should be kept under close observation and the X-ray treatments should be pushed boldly.

In the average case improvement of symptoms has been noted within 24 to 48 hours after the X-ray treatment. It is possible, however, as shown by animal experimentation, to elicit changes in the thymus gland within eight hours after the X-ray exposure. Therefore the most urgent cases can be saved by this treatment.

CONCLUSIONS.

1. 8.4 per cent. of cases show enlarged thymus.

2. Physical examination. History of symptoms are suggestive of diagnosis. X-ray examination is positive evidence.

3. X-ray treatment produces definite cures.

BIBLIOGRAPHY.

1. Paultauf, A.: Wien Klin. Woch., 1889, No. 46; 1890, No. 9

2. Hedinger, E.: Frankfort Zetsch, Path., Vol. 1, p. 527

3. Munch. Med. Woch., 1903, p. 2,090; 1904, p. 785.

4. Archives of Pediatrics: July, 1907, p. 490

5. British Med. and Surg. Journ.: Vol. CLXX, p. 14

THE TREATMENT OF WOUNDS, WITH REFERENCE TO TETANUS PROPHYLAXIS.*

Oscar Berghausen, B. A., M.D.

and

Charles E. Howard, M. D.

Receiving Physician at the Cincinnati Hospital.

Cincinnati.

In June, 1910, the late Dr. N. P. Dandridge proposed the systematic handling of all wounds, punctured, penetrating or lacerated, with the aim of ascertaining the best methods of treating such cases at a large general hospital, particularly with reference to tetanus prophylaxis. As is well known, to avoid the development of tetanus we must begin by treating, in a thorough surgical manner, the wound received. The use of antitetanic serum as a prophylactic agent was resorted to in a large series of cases, in order to test its value.

The following list of instructions were placed in each surgical ward:

The interns will please carry out the instructions mentioned below for the following classes of cases:

1. All perforating, penetrating or lacerating wounds contaminated directly by soil or manure, especially those contracted in the streets or about stables.
2. All blank-cartridge and giant-cracker perforating and lacerating wounds.

INSTRUCTIONS.

1. In all cases above mentioned remove the clothing and foreign material about the wound.
2. Cleanse the surrounding parts with green soap, alcohol, ether and sterile water.
3. Remove with sterile forceps any foreign material lying superficially in the wound.
4. Cleanse the wound with 5 per cent phenol (carbolic acid)-0.5 per cent hydrochloric acid solution.
5. Enlarge the opening by free incision if necessary to thoroughly cleanse the wound, or for the removal of foreign substance.
6. Use a general anesthetic whenever indicated.
7. Pack the wound lightly with gauze soaked in the phenol-hydrochloric acid solution, and dress. Change the dressings daily.
8. Immediately after dressing the wound on the first day give 1,500 units of antitetanic serum subcutaneously. This serum can be obtained at the laboratory.
9. A careful record must be kept and sent to the laboratory when the patient is discharged.
10. In the case of doubt or on the appearance of symptoms resembling tetanus, notify me [Berghausen] at once.

Heretofore such injuries were opened, cleaned and treated with strong phenol solution. The object of using the hydrochloric-phenol mixture as recommended in the text-books was to test its efficiency, since it is attended by less necrosis of tissue. Experience has shown us that treatment of all wounds after the above fashion was sufficient. Particular care was taken to clean out all wounds thoroughly, opening by incision if necessary, to remove all foreign material. Particularly is this necessary in blank-cartridge wounds when wads may have entered. In such cases, in two instances, wads were removed on successive days by different interns, each one thinking that he

had removed the last wad. In these cases a general anesthetic may become necessary.

To ascertain how many wads were present in each blank cartridge, four different specimens were bought and examined. In each one two wads were found, but these were found to be rather loosely made and could easily be torn into fragments.

ANTITETANIC SERUM AS A PROPHYLACTIC MEASURE.

Owing to the experience of others, we have used only one injection of 1,500 units, usually given in that part of the anatomy nearest the wound. We repeated the injection in three cases in which suppuration persisted. In this connection we wish to quote the results of Sir D. Semple,[1] who says:

Many people in apparently good health harbor spores of tetanus in healed wounds or in the intestinal tract, and that hidden away in the tissues the spores remain alive and retain their virulence, but do not grow into toxin-producing bacilli. . . . The leukocytes do not always destroy the spores, but when a local suppuration has ceased they may be able to wander away with the spores still in them. . . . Spore-carriers are in danger of suffering from tetanus (a) on the occurrence of great fatigue or exposure to heat or cold, which diminish their resistance; (b) when the site where the spores are lodged becomes converted into a medium, which from being anaerobic and from a failure of phagocytosis, is favorable for the growth of the spores into toxin-producing bacilli; and (c) when a focus of dead tissue forms in a part of the body at a distance from the site where the spores are lodged.

Quinin given hypodermatically may produce a local tissue necrosis; soluble non-irritating substances do not. Semple further asserts that from 10 to 15 cc. of antitetanic serum renders a patient passively immune for a period of from two to three weeks, and has found it a valuable prophylactic agent when using quinin hypodermatically.

TABLE 1. CASES IN WHICH SERUM WAS USED PROPHYLACTICALLY: GOOD RESULTS.

Character of Injury.	Total No. of Cases	Serum Used, in Units
Punctured wounds (mostly made by nails)	72	1500
Contused and lacerated	4	1500
Cannon-cracker wounds	2	1500
Gun-shot wounds	6	1500
Blank-cartridge wounds	7	1500
Powder burns	5	1500
	96	

SERUM REACTIONS.

These were noted in several cases and were marked by local redness, swelling, urticaria-like eruptions and fever. Owing to patients not reporting as directed, we were unable to obtain complete statistics in this regard. With the aim of preventing such symptoms or of ameliorating them when once developed, atropin sulphate (gr. 1/100-1/120 three times a day, in children less) was given hypodermatically, particularly when numerous injections of serum were made in cases of developed tetanus. We have found that this drug possesses undoubted value in preventing such symptoms. Itching, redness and urticarial eruptions frequently disappeared when atropin was

1. Semple, Sir D.: The Relation of Tetanus to the Hypodermic or Intramuscular Injection of Quinin, Paludism, Simla, January, 1911. No. 2, p. 32.

given. We therefore adopted this measure as a routine before all repeated injections of serum. At times such eruptions will appear following the use of atropin sulphate, but never to a very marked degree.

In Table 1 will be found a list of cases of patients treated at the hospital with the aim of preventing tetanus after the method described in the foregoing.

Not one case of tetanus developed in the above series of patients.

In Table 2 will be found those cases in which serum was not used as a prophylactic measure, and in which the local treatment of the wound was good. Of this list not one developed tetanus.

TABLE 2. CASES IN WHICH SERUM WAS NOT USED PROPHY-
LACTICALLY: GOOD RESULTS.

Character of Injury	No. Cases	Result
Punctured wound—nail	3	Good
Blank-cartridge	3	Good
	6	

In Table 3 will be found those cases in which serum was not used as a prophylactic measure, and which later developed tetanus.

These patients were first seen by us after tetanus had developed, excepting cases 1 and 6. Case 7 occurred in the private practice of Dr. George Krieger, of Madisonville, by whom we were consulted and to whom we are indebted. Case 5 occurred in the service of Dr. Casper Hegner at the City Hospital.

Two cases in which serum was used prophylactically, the one caused by a cannon-cracker wound of the neck and followed by extreme cellulitis before admission; the other, caused by stepping on a nail and followed by cellulitis before admission, resulted in sudden death. No autopsy could be secured, but death was evidently due to an embolus, no symptoms of tetanus developing and no anaphylactic phenomena.

RESULTS WITH AND WITHOUT PROPHYLACTIC SERUM TREATMENT.

In the ninety-six cases properly treated locally and by the prophylactic administration of antitetanic serum, not one patient developed tetanus.

In the fourteen cases (Tables 2 and 3) treated without the prophylactic administration of antitetanic serum, eight patients developed tetanus, of whom six died.

In the cases (only six, however) properly treated locally and without the prophylactic administration of antitetanic serum, not one patient developed tetanus.

Patient 6 (Table 3) was thoroughly treated locally, but did not receive the prophylactic serum injection and succumbed to tetanus.

We had the opportunity of assisting in the treatment of eight patients with developed tetanus during the past fifteen months, and feel that the information gained is of some value. The usual methods of treatment were employed, antitetanic serum and phenol subcutaneous injections (2 per cent.) included. Briefly stated, our observations are as follows:

Although the cases with a short incubation period offer the least hope, such cases are not necessarily fatal. Case 7 was seen by Dr. Krieger, the first physician consulted in the case, two days after symptoms of tetanus had developed, and yet the manifest symptoms disappeared after one week's careful treatment.

If antitetanic serum is to be used at all, large doses must be employed, although enormous doses, as recommended by those interested in its sale, were not used by us.

Atropin sulphate has some value in controlling serum reactions and is deserving of further trial.

TABLE 3. CASES IN WHICH SERUM WAS NOT USED PROPHYLAC-
TICALLY AND TETANUS DEVELOPED.

Cases	Character of Injury.	Incubation Period (days)	Early Treatment of Wounds	Serum (in units) Used Therapeutically (Sidenta neous)	Carbolic Injections	Phenol Acid in gm	Albuminuria	Duration of Illness	Result
1	Multiple puncture wound made by shot	7	—	0	0	—		14 hours	Death.
2	Lacerated wound	4	—	20,000	0.24	+		5 days	Death.
3	Punctured wound (nail)	5	—	0	0.14	+		30 hours	Death.
4	Punctured wound (pick-ax)	8	—	3,000	0	—		4 days	Death
5	Cut by a barbed wire	14	—	50,000	0	—		14 days	Recovery.
6	Crushed foot	10	+	27,000	0			2 days	Death.
7	Cut by a scythe	8	0	27,000	0	—		About 2 wks.	Recovery.
8	Compound fracture; infected	6	—	27,000	0	?		2 days	Death.

*In this column + means "good," — means "poor" and 0 means "none" ; In this column + means "present," — "absent" and 0 "doubtful."

The subcutaneous administration of phenol, 2 per cent. solution, is followed by an early appearance of albumin in the urine. This possibility of damaging the kidneys must be taken into consideration when the injections are used. In the future we shall follow such injections by the rectal administration of a hypertonic neutral salt solution to limit, if possible, this damage to the kidneys, in accordance with the results obtained in experimental nephritis, by Prof. Martin H. Fischer, of this city.

We feel, after a careful study of such injuries as listed in the foregoing, that no wound of such a nature should be treated lightly by any physician. By carefully cleansing each wound, using a general anesthetic if necessary to remove all foreign material, and employing a diluted antiseptic to prevent sepsis, and then treating each one as an open wound, the physican has done much to prevent tetanus. By employing one immunizing dose of 1500 units of antitetanic serum, to be repeated only when suppuration has not ceased after a week, he can practically assure the patient perfect safety from tetanus.

THE EARLY RECOGNITION OF HYDROCEPHALUS IN MENINGITIS.*

Kenneth D. Blackfan.

Baltimore.

Interference with absorption of the cerebrospinal fluid in acute meningitis may be brought about by an exudate so localized that it obstructs the foramen of Magendie and the foramina of Luschka, or the exudate may block, partially or completely, the cisternae (magna, interpeduncularis and pontis) at the base of the brain and so prevent the free distribution of cerebrospinal fluid throughout the cerebal subarachnoid space. The spinal subarachnoid space may be filled partially or completely with exudate, thus limiting the participation of this surface in the absorption of the cerebrospinal fluid. Various combinations of these processes may coexist. In any event, if the absorption of cerebrospinal fluid is diminished for a sufficient length of time, hydrocephalus is produced.

A brief discussion of the formation and the circulation of the cerebrospinal fluid and the more recent information concerning hydrocephalus will not be out of place here.

Cerebrospinal fluid is formed within the ventricles from the activity of the choroid plexus. Under normal conditions it passes from the ventricles through the various foramina (foramen of Magendie and foramina of Luschka) to the subarachnoid system where it is absorbed. Absorption in the ventricular system is negligible. From the subarachnoid system the cerebrospinal fluid is absorbed directly into the blood stream. Although absorption takes place from both the cerebral and the spinal subarachnoid systems, cerebral absorption is much greater than spinal absorption. This is due to the fact that the cerebrum offers a much greater absorbing surface and that a more extensive blood vascular area is exposed to contact with the cerebrospinal fluid. Disproportion between the formation and the absorption of cerebrospinal fluid results in its accumulation and its retention within the ventricles.

Hydrocephalus is secondary to some process that interferes with the normal circulation or absorption of cerebrospinal fluid. Anatomically, two types have been demonstrated: (a) obstructive, and (b) communicating. Obstructive hydrocephalus develops because the cerebrospinal fluid cannot pass from its place of origin in the ventricles to the cerebral and spinal subarachnoid space where absorption takes place. Communicating hydrocephalus—the channels of communication between the ventricles and the spinal subarachnoid space being patent to a greater or less degree—results because the cerebrospinal fluid cannot reach the cerebral subarachnoid space where the greater part of absorption takes place. In the majority of instances this

is due to adhesions which obliterate the various cisternae or centers from which the cerebrospinal fluid is distributed over the cortex of the brain. A combination of the two types may result if, in addition to interference with the absorption of the cerebrospinal fluid from the subarachnoid space, there is an inadequate communication between the ventricular and the subarachnoid system.

The primary cause of chronic hydrocephalus in a series of cases studied recently was a previous meningitis in fourteen cases, a congenital absence of the aqueduct of Sylvius in three cases and a tumor blocking the iter in one case.

A differentiation between the two types of hydrocephalus by clinical signs alone is difficult, as the symptoms produced are essentially alike. The type of hydrocephalus may be suggested by the amount of cerebrospinal fluid that is obtained by lumbar puncture. Increase in amount of cerebrospinal fluid in acute infection of the meninges, the influence of posture on the amount of fluid obtained and alteration in the pressure in the cerebrospinal system have to be taken into consideration before drawing conclusions from the results of lumbar puncture alone. The two types of hydrocephalus can be differentiated, however, by the phenolsulphonephthalein test. When phenolsulphonephthalein is injected into the ventricle in obstructive hydrocephalus, the dye does not appear in the cerebrospinal fluid obtained from the lumbar subarachnoid space within forty minutes, if at all. In patients who do not have hydrocephalus and in those with the communicating type of hydrocephalus, the phenolsulphonephthalein appears promptly (in from six to twelve minutes). When phenolsulphonephthalein is injected into the lumbar subarachnoid space in communicating hydrocephalus, absorption of the dye is greatly lessened. Less than 20 per cent. is excreted in the urine within two hours, as compared to 35 or 60 per cent. in normal persons. In obstructive hydrocephalus, when the cisternae and the meninges are not affected, absorption is as prompt as in normal individuals. The phenolsulphonephthalein test has been employed in the study of a comparatively large number of patients with chronic hydrocephalus, and when carried out properly it affords accurate information regarding the patency of the foramina between the ventricles and the subarachnoid system and the amount of absorption from the subarachnoid space. Recently Dandy[1] suggested that cerebrospinal fluid removed from the ventricle by ventricular puncture be replaced by air. When this is done and a roentgenogram is made, the ventricles appear clearly outlined. By this procedure a hydrocephalus can be demonstrated and its extent measured.

It has long been known that hydrocephalus is a frequent complication of meningitis, but until recently there has been no means by which its early recognition has been possible or a differentiation between the two types of

1. Dandy, W. E.: Ann. Surg. 68:569 (Dec.) 1918. Also: Am. J. Roentgenology n:26 (Jan.) 1919; Bull. Johns Hopkins Hosp. 30:29 (Feb.) 1919.

hydrocephalus could be made, both of which are essential for successful treatment

In the present study I have carried out the phenolsulphonephthalein test[2] in patients with meningitis in which hydrocephalus has developed, and I have had roentgenograms made after the injection of the ventricles with air.[3] Particular attention has been paid to the early diagnosis of hydrocephalus and to the pathologic findings. Twenty-five cases of hydrocephalus were studied.

Meningitis due to the streptococcus, the *Staphylococcus aureus*, the influenza bacillus and the pneumococcus is a terminal manifestation in the majority of instances, secondary to a primary focus elsewhere. The entire course of the meningitis is usually of short duration, which explains the infrequency of hydrocephalus in meningitis due to these organisms. Hydrocephalus was observed, however, in the course of a meningitis due to the influenza bacillus in two patients, four and eight months of age, respectively. They lived about two weeks. A communicating hydrocephalus was demonstrated at necropsy in one patient, and an obstructive hydrocephalus in the other. In the latter, the hydrocephalus was suspected, as it was impossible to obtain more than a few drops of cerebrospinal fluid by lumbar puncture. The phenolsulphonephthalein test showed that an obstruction existed between the ventricular and the subarachnoid systems, and at necropsy the basal foramina were found to be obstructed by a thick purulent exudate

The infrequency of hydrocephalus in tuberculous meningitis is due, probably, to the relatively slight involvement of the meninges. It is only occasionally that the exudate is so situated or sufficiently large in amount to interfere with the avenues of exit of the cerebrospinal fluid from the ventricles or to diminish the absorption from the subarachnoid space by involving the cisternae at the base of the brain. In tuberculous meningitis two cases of communicating hydrocephalus were demonstrated. In each patient phenolsulphonephthalein appeared promptly in the lumbar subarachnoid space after its introduction into the lateral ventricle, but absorption from the subarachnoid space was greatly diminished. At the necropsy the basal foramina were found to be patent, but absorption was limited to the spinal subarachnoid space by an exudate involving the cisternae. In four cases the hydrocephalus was of the obstructive type. In these patients, phenolsulphonephthalein did not appear in the lumbar subarachnoid space after its injection into the ventricles. The foramina of exit at the base of the brain were obliterated by a tuberculous exudate in these cases.

The majority of the cases of hydrocephalus occurred in meningococcus meningitis. Of twenty-five cases occurring in the course of acute meningitis, seventeen were due to the meningococcus. Communicating hydrocephalus

developed in eight of the seventeen cases, and in nine the obstructive form was found. Ten of the seventeen patients in this series died and seven recovered. Two of the seven patients had an obstructive hydrocephalus and improvement followed promptly after the introduction of antimeningo-coccus serum into the ventricles. In four cases in which a communicating hydrocephalus was present, the process became arrested after treatment. The patients made an uneventful recovery. One patient developed a chronic hydrocephalus (communicating). He was three months old and was first seen twenty-four hours after the onset of the meningeal symptoms. Meningococci were grown from the blood and the cerebrospinal fluid. Antimeningococcus serum was administered intravenously and into the lumbar subarachnoid space. After the first few days the meningococci disappeared for a time from the cerebrospinal fluid. The temperature remained irregular. The meningeal symptoms did not disappear, and from time to time, in spite of treatment, the organisms would reappear in the cerebrospinal fluid. He was treated intensively with serum introduced into the ventricles and the lumbar subarachnoid space over a period of twenty-four days before the meningococci disappeared permanently and the cerebrospinal fluid became normal. Seven months after the onset of the meningitis, the head was greatly enlarged and a ventriculogram showed almost complete destruction of the cortex (Fig. 1). The patient is alive at the present writing.

A necropsy was performed in the ten fatal cases, and the clinical diagnosis was confirmed by demonstration of the exciting cause of the hydrocephalus. In seven cases (obstructive hydrocephalus) an exudate occluded the foramina at the base of the brain, and in three cases (communicating hydrocephalus) the basal cisternae were totally obliterated by a thick purulent exudate. Whether an exudate or adhesions are found at necropsy in this form of meningitis depends primarily on the duration of the disease.

It is not within the province of this paper to discuss the pathologic process met with in the various types of meningitis. Acute hydrocephalus in meningitis develops because, as in chronic hydrocephalus, there is a diminution in the absorption of the cerebrospinal fluid. The important point to recognize is that the lesion must be so located as to obstruct the outflow of cerebrospinal fluid from the ventricles to the subarachnoid space, or else to limit the area of absorption from the spinal or cerebral subarachnoid system. The disappearance of the exudate and the formation of adhesions determine the transition from an acute to a chronic hydrocephalus, and the re-establishment of an equilibrium between the formation of cerebrospinal fluid and its absorption determines whether the process will become arrested or advance progressively. The chronicity of meningococcus meningitis makes it the form of meningitis par excellence for the development of a chronic hydrocephalus. Meningitis due to other organisms almost without exception is fatal, and in a short time.
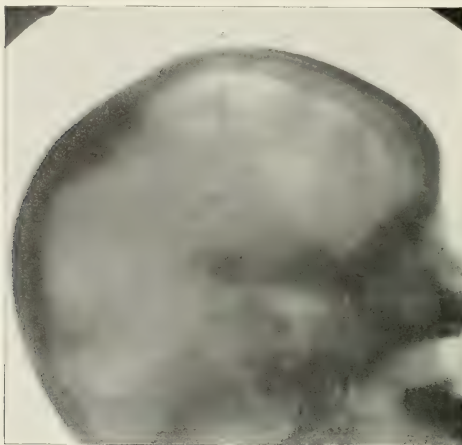
Fig. 1. Roentgenogram taken seven months after the onset of an acute attack of meningococcus meningitis. The phenolsulphonephthalein test showed that there was a free communication between the ventricles and the spinal subarachnoid space. Absorption from the subarachnoid space was 9 per cent. in two hours. After air injection the roentgenogram showed the lateral ventricles to be markedly dilated (A) and an extreme grade of atrophy of the cortex (C).

TABLE 1. ACUTE HYDROCEPHALUS IN MENINGITIS.

Type of Meningitis	No. of Cases of Meningitis with Hydrocephalus Studied	Type of Hydrocephalus	
		Obstructive	Communicating
Influenza bacillus	2	1	1
Tubercle bacillus	6	4	2
Meningococcus	17	9	8
Total	25	14	11

Attention may be directed to a hydrocephalus developing in meningitis by the onset of certain symptoms. The diagnosis is readily established when the condition is of long duration and the symptoms of increased intracranial pressure—headache, stupor, vomiting, enlargement of the head and changes in the eye grounds—are present. The early manifestations of hydrocephalus, however, are so closely interwoven with the symptoms of the meningitis itself, that they are often difficult to recognize. Hydrocephalus should always be suspected with the persistence of symptoms of meningeal irritation (fever, hyperesthesia, irritability or drowsiness, rigidity of the muscles of the neck and extremities, hyperactive reflexes, tremors, etc.) or their reappearance after the symptoms of meningitis have subsided. Infants invariably have a tense and bulging fontanel and in children, Mac-

ewen's sign is positive. It should be remembered that these symptoms cannot always be referred to the hydrocephalus alone. We often see at the onset of acute meningitis and throughout the course of the disease manifestations indicative of increased intracranial pressure—headache, fever, vomiting and muscular rigidity—which do not mean necessarily that hydrocephalus is present. I believe that much confusion has been caused by referring to such a condition as hydrocephalus. For instance, in tuberculous meningitis there is present quite constantly a marked increase in the amount of cerebrospinal fluid, but at necropsy a picture quite the reverse of that seen in hydrocephalus is found. The sulci are distended with fluid, the brain is edematous, and though there is a varying increase in the size of the ventricles, one does not find flattening of the convolutions, atrophy and compression of the brain substance and the marked dilatation of the ventricles which characterize the latter condition. A number of patients with tuberculous and meningococcus meningitis who presented such symptoms have been studied by determining the amount of cerebrospinal fluid withdrawn, by the phenolsulphonephthalein test and the pathologic findings at necropsy. In these patients there was no interference with the absorption of cerebrospinal fluid and at necropsy the findings characteristic of hydrocephalus were not present. It is not at all likely that an increase in the amount of cerebrospinal fluid can produce other than a temporary and insignificant hydrocephalus, unless there is an associated diminution in the absorption of the fluid. The results are shown in Table 2.

Abnormal changes in the eye grounds and enlargement of the head, when present, are symptoms indicative of an hydrocephalus, but they are seldom seen early in its development and so are of but little aid in making the diagnosis. This is especially true before the fontanels are closed and the

TABLE 2. FINDINGS IN CASES OF MENINGITIS WITH INCREASED INTRACRANIAL PRESSURE, BUT NO HYDROCEPHALUS.

Case	Diagnosis	Phenolsulphonephthalein Tests		Spinal Fluid		Necropsy
		Absorption from Sub-arachnoid, per cent.	Patency of Communication, minutes	Pressure	Amount C.c.	
1	Tuberculous meningitis	45	10	Increased	40	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.
2	Tuberculous meningitis	40	12	Increased	55	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.
3	Tuberculous meningitis	38	8	Increased	35	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.
4	Tuberculous meningitis	42	11	Increased	45	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.
5	Meningococcus meningitis	55	12	Increased	50	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.
6	Meningococcus meningitis	48	13	Increased	40	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.
7	Meningococcus meningitis	62	10	Increased	45	Ventricles not dilated. Exudate slight, not involving the basal foramina or cisternae.

sutures are firmly united. A considerable atrophy and compression of the brain takes place before the intraventricular pressure becomes sufficient to cause marked changes in the eye grounds and an enlargement of the head. This is well illustrated in the case of an infant, three months of age, who was observed from the onset of an acute meningococcus meningitis throughout the various stages of development from an acute to a chronic hydrocephalus. This is graphically shown in Table 3.

Table 3. FINDINGS IN A CASE OF ACUTE MENINGOCOCCUS MENINGITIS DEVELOPING FROM AN ACUTE TO A CHRONIC HYDROCEPHALUS

				Phenol-sulphone-phthalein Tests		
Duration of Disease	Circumference of Head	Eye Grounds	Roentgenogram of Ventricles	Patency of Communication	Absorption from Sub-arachnoid Space	Symptoms
Onset	44 cm	....	....	....	....	Collapse, fever, depressed fontanel, petechiae.
1 mo.	44 cm	Normal	.. . .	....	....	Bulging fontanel, rigidity, hyperesthesia.
2 mo.	44 cm	... .	... .	....	....	Bulging fontanels, rigidity, opisthotonus.
3 mo.	+1 3 cm	Slight dilatation of retinal vessels. Margin of disk clear. Normal physiologic cupping.	Ventricles dilated. Marked cortical atrophy.	–	9%	Bulging fontanels, rigidity, opisthotonus.
4 mo.	+.. 7 cm	Same	Same	r	..	Opisthotonus disappeared, vomiting, tense fontanels.
7 mo.	19.5 cm	Same	Practically no cortex seen. Ventricles greatly enlarged.	. . .	....	Bulging fontanels, separation of sutures, craniotabes, rigidity, vomiting, emaciation

The amount of cerebrospinal fluid obtained by lumbar puncture affords the most helpful clinical sign of hydrocephalus, although, as previously mentioned, it is not absolutely dependable. In hydrocephalus the cerebrospinal fluid is under greatly increased pressure and an abnormal amount is obtained readily or it is obtained in small amount and with difficulty.

A definite increase in the amount of cerebrospinal fluid of 50 cc. or more, withdrawn repeatedly when the other signs of the acute infection of the meninges have subsided, is significant of a communicating hydrocephalus. While this is suggestive evidence, it is not sufficient in itself to establish the diagnosis, as relatively large amounts of cerebrospinal fluid are sometimes found in obstructive hydrocephalus.

Small amounts of cerebrospinal fluid obtained by lumbar puncture suggest an obstructive hydrocephalus. If the subarachnoid space has been entered, and the fluid is not too thick to run through the needle, it is relatively safe to conclude that there is an exudate so situated as to prevent the free flow of cerebrospinal fluid from the ventricles to the spinal subarachnoid space. In obstructive hydrocephalus relatively large amount of cerebro-

spinal fluid may be recovered at the first lumbar puncture and then the
quantity lessens so that only a few drops are obtained at successive punc-
tures (Fig. 2). Corroborative evidence of the presence of hydrocephalus
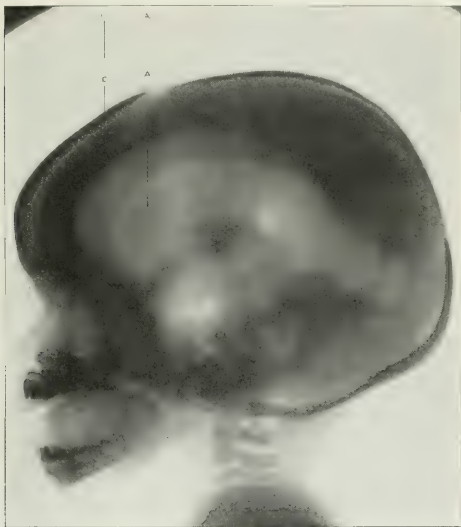
Fig. 2. Obstructive hydrocephalus in a patient aged three months. The onset
of the hydrocephalus was suggested by the persistence of the symptoms of meningitis.
The cerebrospinal fluid was obtained readily for ten days and then only a few drops
flowed from the needle. The phenolsulphonephthalein test showed that there was no
communication between the ventricles and the subarachnoid space. Absorption from
the subarachnoid space was 55 per cent. in two hours. After air injection the roentgen-
ogram showed dilated lateral ventricle (A) with atrophy of the cortex (C).

may be shown by the results from puncture of the ventricle, as in such cases
the cerebrospinal fluid in the ventricles is under increased pressure and an
excessive amount can be withdrawn.

The early recognition of hydrocephalus is of practical importance in
meningitis due to the meningococcus. Many cases of hydrocephalus, the
result of meningococcus meningitis, are reported in the literature in which
the hydrocephalus developed despite treatment with antimeningococcus
serum. In the majority of instances this has occurred when treatment was
instituted late, for the outcome at this stage of the disease, even with appro-

priate treatment is uncertain (Fig. 3). The earlier and the more intensive the treatment, the better the chance of recovery. In obstructive hydrocephalus if the serum is introduced only by lumbar subarachnoid injection there is the danger of organization of the exudate and also that the meningococci remaining in the ventricles are not subjected to the influence of the serum. In this form of hydrocephalus the antimeningococcus serum should be injected directly into the ventricle as well as into the lumbar subarachnoid
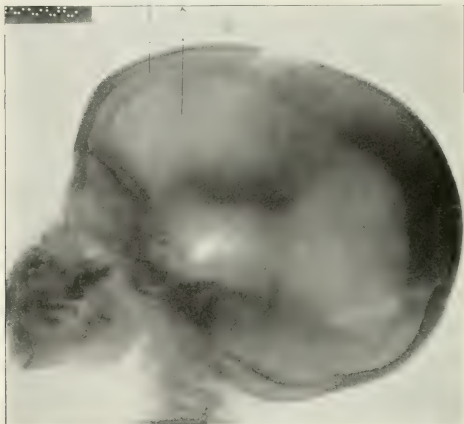
Fig. 3. Communicating hydrocephalus in a patient, two years old, who was untreated for six weeks following the onset of an acute meningococcus meningitis. Examination showed rigidity of the neck, positive Kernig's sign and a low grade optic neuritis. The phenolsulphonephthalein test showed that there was a free communication between the ventricles and the subarachnoid space. Absorption from the subarachnoid space was 8 per cent. in two hours. After air injection the roentgenogram showed dilated ventricles (A) with atrophy and compression of the cerebral cortex (C). The patient died in spite of the administration of antimeningococcus serum into the ventricles and into the lumbar subarachnoid space.

space. In communicating hydrocephalus intraventricular injection of serum also is advisable. A larger amount may be injected and thereby brought into direct contact with the exudate and in greater concentration than by the lumbar subarachnoid injection alone. (Fig. 4.)

The capacity of the meninges to absorb cerebrospinal fluid should be tested by the lumbar subarachnoid injection of phenolsulphonephthalein, when the symptoms of meningeal irritation persist or when they reappear after the vigorous use of antimeningococcus serum. A distinct diminution in the absorption of cerebrospinal fluid indicates a communicating hydro-

cephalus. This diagnosis can be confirmed by determining the patency of the foramina between the ventricular and the subarachnoid systems by the injection of phenolsulphonephthalein directly into the ventricle. If the symptoms are the result of an obstructive hydrocephalus the absorption of the cerebrospinal fluid from the lumbar subarachnoid space will not be
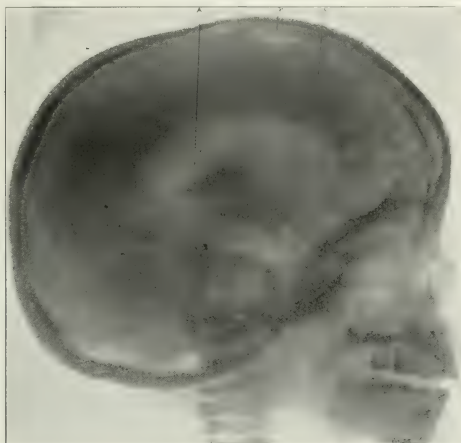
Fig. 4. The patient, aged three years, was treated for two weeks with antimeningococcus serum. He did not improve and meningococci persisted in the cerebrospinal fluid. The phenolsulphonephthalein test showed that absorption from the subarachnoid space was diminished (13 per cent. in two hours). Ventricular injection of the dye through a trephine opening demonstrated a communication between the ventricles and the lumbar subarachnoid space. After air injection the roentgenogram shows enlarged lateral ventricles (A), the trephine opening (B) and compression and atrophy of the cerebralcortex (C). After three injections of antimeningococcus serum into the ventricles, the organisms disappeared. The patient made an uneventful recovery.

diminished. The diagnosis in this type of hydrocephalus will then depend on the nonappearance of phenolsulphonephthalein in the lumbar subarachnoid space after its injection into the ventricle. These tests add nothing to the severity of the treatment. They do not demand any unnecessary operative procedure, as under such circumstances it is necessary to bring serum, either through an open fontanel or through a trephine opening, in so large an amount and in as concentrated a form as possible, directly in contact with the purulent exudate at the base of the brain.

STANDARDS OF SUCCESS IN MEDICINE.*

George Emerson Brewer.

In accepting the invitation of our President to be present at the annual opening exercises of the medical school and say a few words to the entering class, I was somewhat at a loss to determine what subject I should choose which might be of interest. I take it, that in an address of this kind an effort should be made to suggest some thoughts which will be helpful to the entering student in arranging his time and studies or informulating plans for his future work, and in addition to remind him of the responsibilities which he is to assume, the difficulties he will encounter, and the kind of success he may hope to attain.

As I look about me and study for a moment the new and unfamiliar faces, differing as they do in many respects and conveying to my mind differences in character, temperament, previous training, and the ability to work, I feel that they express one thing in common, namely, a determination to begin in earnest the real business of life. In the preparatory schools and colleges your intellectual burdens have been lightened by a judicious admixture of recreation, sport, and mutual companionship; you have enjoyed long periods of vacation, and at no time have been driven under high pressure toward the attainment of a single object, upon which will depend the measure of your success in life. Here in the medical school all will be changed: you will find conditions materially altered, you will be surrounded by an atmosphere surcharged with enthusiasm and active competition. Soon you will realize that to win a prize or even to receive an honorable mention in the professional race with your colleagues, you must at least secure at the end of your college course a creditable hospital appointment. To obtain this you must early acquire and persistently maintain a high rank in your class, and this means hard, enduring, concentrated work, not a few hours each day, but from ten to twelve or fourteen hours out of each twenty-four of the college year, and the willingness to devote at least one-third to one-half of your summer vacations to clinical work in the various hospitals and dispensaries of the city. If these conditions seem too severe, better matriculate at once in some other medical school, for here at the College of Physicians and Surgeons our standards are high, our student body far above the average in intelligence and training, and the pace set by the leaders of each class exceedingly difficult to maintain, but we firmly believe that the rewards open to the successful student are well worth the effort.

This thought suggests the inquiry why so many young men, well equipped for almost any professional or business career, choose annually to cast their lot with the medical fraternity. It is certainly not with any hope of amassing a fortune, for if you do not already know it, it is only fair for me to

assure you that the practice of medicine offers little or no hope of great financial return.

What then are the rewards of a life devoted to the study and practice of medicine? What are the reasons why you have elected to devote your lives to a profession which offers so little of pecuniary reward even to the most successful of its followers? I take it that the reason why so many capable young men enter our profession is that they hope for and expect a reward which cannot be reckoned in dollars and cents, but which will outweigh in real value the benefits to be derived from the accumulation even of great wealth.

This brings me to the announced subject of my informal talk with you this morning: What are the standards of success open to the practitioner or student of medicine? Time will permit me to mention only a few, and these I can best illustrate by examples. Take in the first place the practitioner of internal medicine, the man whose relationship to his patient is that of the family physician. Those of you who are familiar with the charming essays and character sketches of Maclaren, will recognize as one of the best of this type, the rugged resourceful old Scotch physician, William MacLure, a doctor of the old school, who preferred to practice his profession in the highland glen of his birth to accepting an honorable position in one of the great medical centers. For forty years, day and night, summer and winter, in sunshine and storm, through snow, ice, drifts and floods, he visited the sick and injured of his own village and the scattered dwellers of the glen. It is true, MacLure was but a character of fiction, created as a composite type from the lives and virtues of hundreds of his class in all parts of the civilized world—the type of man who gives all that he possesses in kindliness, sympathy, and helpful assistance for a lifetime, and receives in return only sufficient coin of the realm to keep a roof over his head, food and clothing for his body, but such a harvest of esteem, appreciation, gratitude and affection, as to fill to overflowing every desire of his generous heart.

Let us, however, turn from the hard conditions of life of our rugged Highland practitioner, to the softer paths of one of his more fortunate brothers. I have in mind the career of one of the greatest consultants and teachers of medicine of our times. Reared amid scholarly surroundings, graduating in medicine at an early age, he quickly rose to a commanding position in the medical world. The master word of his early training seemed to be work: constant, conscientious, concentrated, and systematic work. By this means he early acquired an enormous fund of medical knowledge, and in addition so trained his mind to accurate observation, accurate deduction, and accurate speech, as to fit himself admirably for the rôle of teacher, in which he later became so successful. To watch him on his hospital visits was a liberal education; the carefully elicited history, the accurate and painstaking physical examination, the judicious employment of laboratory aids, and finally the logical summing up of the evidence, his masterly

analysis of the symptoms and signs of the disease leading to the establishment of an accurate diagnosis, as well as his safe and sane suggestion in regard to treatment, made him one of the great clinicians of his time. The sterling qualities of his mind, his great industry, his charming personality, his magnetic enthusiasm and withal his keen sense of humor, would have made him a conspicuous success in any walk of life or field of human endeavor. In medicine few if any practitioners ever reached the measure of professional success which he achieved; and no teacher ever inspired in his students more lofty ideals, more enthusiastic devotion to work, or more loyal affection for their chief. William Osler never prized, sought after, or accumulated wealth. He always preferred an autopsy to a consultation, and almost invariably would refuse an out-of-town summons from a wealthy client if it interfered with his hospital rounds or a morning with the students. In his mental and moral make-up, there was never any suggestion of commercialism, yet his professional success was so great as completely to overshadow any thought of financial reward.

It is perhaps the general surgeon whom the world looks upon as reaping the highest financial rewards in the medical profession, and yet one seldom hears of a surgeon whose period of large returns lasts more than a few years. Of all the surgeons of my acquaintance, the one whose life seemed to himself and his associates most rounded and filled with professional satisfaction and success, was a man born amid the humblest of surroundings in a small New England hamlet. With educational opportunities of the most limited character, by extraordinary industry, undaunted courage, and an unlimited capacity for work, he raised himself to one of the foremost position in surgery of his time. Cast in a heroic mould, with fine constitution and superb health, he began his practice in a western city, and learned his surgery by hard personal experience. Receiving his degree long before the antiseptic era, he, in common with all others practicing surgery at that time, soon became familiar with the almost universal septic disasters which followed surgical operations, and yet by keen judgment and by an almost superhuman surgical intuition, he seemed to avoid in a remarkable degree the fatalities which followed the work of others. His success inspired wide confidence, and as a result of his sterling integrity, kindly manner and great-hearted sympathy, the members of the community in which he lived, almost without exception, turned to him in their surgical emergencies. No operation offering a reasonable hope of success was too difficult for him to undertake; no sacrifice was too great for him to assume, if it contributed to the well-being or comfort of his patient; and no man or woman was too poor to insure his best efforts. His talents were soon recognized, and while still a young man he was appointed professor of surgery in a flourishing medical school. His reputation grew rapidly, his skill was constantly in demand, by the rich and poor alike, not only of his own city, but throughout the greater part of his own and neighboring states. His contributions to abdominal surgery, then

in its infancy, his improvements in operative technic, and his ingenuity in devising new and improved methods of operating and wound treatment gave him a national reputation. I never knew a man whose life was so full of anxious work; his expenditure of energy would quickly have disabled a man of less vigorous constitution. Although he enjoyed for his day a large income from his wealthy patients, more than half his time and effort was devoted to the less fortunate members of society, from whom he received little or no compensation. One day in the height of his professional success, he was called upon by a physician of his acquaintance who asked him if he would operate upon a man with strangulated hernia. He explained that it was impossible on account of a college lecture and an afternoon filled with appointments and urgent consultations. His colleague replied that it was unfortunate for the patient, who refused to go to a hospital or allow any one else to operate. The surgeon hesitated, then inquired if the man had money. "No," was the reply, "only an invalid wife and a large family of children." "Then I will go," was the reply; "poor devil, if he had money he could get some one else." Quickly canceling his engagements, he gathered his assistants, went to the poor man's home, and performed a successful operation. In performing the operation, successful for the patient, the operator accidentally pricked his finger with a needle. That needle-prick ended the career of this talented great-hearted surgeon—not by a quickly fatal infection with moderate suffering, but by a long-drawn-out, discouraging and progressively weakening malady; for the virus entering the veins by this insignificant needle prick was the venom of syphilis. Occurring at a time when the disease was little understood, and treated with less success than at present, with the kindly assistance of his professional colleagues he battled with the virulent infection for weeks, months and years, only to develop at the end the gravest type of cerebral disease. He died a mental and physical wreck. You may ask why I mention the career of this unfortunate man as an example of professional success. I mention it not only on account of his valuable contributions to surgery for twenty-five years, but chiefly for the reason that every act of his generous life was, like the immediate cause of his untimely death, inspired by an unmeasured amount of human sympathy and love for his fellowmen.

Before closing I feel that I must say just a word in regard to the opportunities for professional success offered by the laboratory worker, the investigator, the seeker after the great truths which nature seems so maliciously to conceal. The poorest paid of all, this unselfish and self-sacrificing army of scientific workers seems content, without hope or thought of pecuniary reward, to devote their lives to the study of the nature and causation of disease, the etiology of infection, the pathology of new-growths, the underlying principles of immunity, the function of the ductless glands, the synthetic elaboration of remedial agents, the explanation of shock, the development of new and safer methods of anesthesia, surgical technic and

the hundred other problems of vital interest to the practitioner. The work is arduous, time consuming, exhausting, yet the rewards are great.

Take the life of Jenner, the English country doctor, living in the last century at a time when the great civilized centers of Europe were annually devastated by the most dreaded of all modern plagues, epidemic smallpox. He made up his mind to investigate its cause and, if possible, to discover a remedy for it. He began to study it carefully from all points of view, and his attention by a strange coincidence was quickly directed to a similar disease which prevailed among cattle. Mildly toxic in character, it was accompanied by lesions which were almost identical with those of smallpox. Dr. Jenner also discovered that the people who had care of these cattle, as milkmen and stablemen, were often infected and presented small lesions on their hands, and that these people were absolutely and forever immune from smallpox. Then a great idea entered his mind: if the entire community could be inoculated with this mild cowpox, no epidemic of smallpox could affect them. This idea grew in the mind of Jenner, and developed into a great principle of medical therapeutics. When he was bold enough to announce his discovery before the Royal College of Physicians of London, did they receive it with enthusiastic interest or open minds? Not at all—on the contrary, they denounced Dr. Jenner, called him a quack, a charlatan, declared that his methods were brutal and inhuman and should never be included in scientific medical practice. Jenner, however, persisted in advocating protective vaccination, and was finally enabled to prove the truth of his discoveries. He died a poor man. Although he devoted the greater part of his professional life to this great work, if it had not been for the liberality of the British government he would have died in abject poverty. Today what millionaire, what multimillionaire, would not give the greater part of his possessions for a name and fame like that of the great Jenner?

Let us turn for a moment to the career of Pasteur, a trained chemist, who in early life gave evidence of great originality of thought. Pasteur thought he saw in fermentation the action of living germs, low forms of animal and vegetable life. As he studied fermentation, he actually discovered in fermenting substances millions of these organisms, differing in size and shape with the various types of fermentation. Later he recognized that the processes he observed during the fermentation of inert matter were similar to the processes which take place in human beings and animals as a result of infectious disease. Then a great idea occurred to him, namely, that these or similar micro-organisms were the cause of infectious diseases. By his logical reasoning, his accurate methods of investigation, and his epoch-making inoculative experiments, he demonstrated the great truth of the causation of contagious diseases, namely, that they are due to the presence in the blood and tissues of these low forms of animal or vegetable life—and the great germ theory of disease was born. As a reward, did Dr. Pasteur receive the generous treatment of his medical colleagues? Decidedly not.

He was more bitterly denounced and criticized than was Jenner; but he knew he was right because his methods were accurate; he was convinced that his logical deductions could not be disproven, and he finally was able to demonstrate to the scientific world that his theories were absolutely correct. On the occasion of the celebration given in honor of his seventieth birthday by the French government, before an enormous audience composed of distinguished men of science from all parts of the civilized world, the great Lister, addressing him, said: "You have raised the veil which for centuries has covered infectious diseases. You have discovered and demonstrated their microbic origin." Dupuy, a colleague, said: "Who can say how much human life owes to you, and how much more it will owe to you in the future." J. B. Dumas, his friend and admirer, said: "May Providence long spare you to France, and maintain in you the admirable equilibrium between the mind that observes, the genius that conceives, and the hand that executes with a perfection and accuracy hitherto unknown." Apart from his epoch-making discoveries, Pasteur blazed the trail for all future investigation by demonstrating the immense value of painstaking accurate laboratory methods in the elucidation of the many biological and pathological problems which have confronted and which are today confronting the medical world. As a result of the powerful stimulus given to all scientific work by his methods and success, and the many problems suggested by his demonstration of the microbic nature of infectious diseases, hundreds of able workers have been attracted to this fruitful field of investigation, and medicine has been enriched by the masterly work of Koch, of Roux, of Behring, of Kitasato, of Ehrlich, of Widal, of Wright, of Welsh, of Flexner, and a host of others equally distinguished.

It is, however, to the work of Lister that surgeons turn with superlative pride and with the greatest satisfaction. Practicing surgery in the pre-antiseptic days, he quickly appreciated that the greatest factor in the prevention of surgical progress was infection—not at that time known by that name or understood, but recognized on every side by its final results, suppuration, wound fever, pyemia, septicæmia, erysipelas, hospital gangrene, etc., etc. The death rate from this cause following surgical procedures was so great, that only a few necessary life-saving operations were undertaken, as the repair of severe injuries, amputations for malignant disease, ligation of vessels for hemorrhage or aneurism, and the occasional removal of disfiguring tumors. The death rate following major amputations was upwards of 60 per cent., of strangulated hernia 40 to 60 per cent., of abdominal section almost 100 per cent. In not a single instance in one hundred years at the Vienna Maternity Hospital had a woman survived Cæsarean section, an operation you will frequently see at the Sloane Hospital with practically no mortality. Nelaton, who was in despair during the siege of Paris, at the sight of the death of nearly every patient operated upon at the Grand Hotel, then a temporary military hospital, declared that the surgeon who could con-

quer purulent wound infection would be deserving of a golden statue. Lister's great mind saw in Pasteur's work an explanation of surgical infection. He believed septic disease to be due to the presence in the tissues of pathogenic bacteria, and he conceived the great idea that if those microorganisms could be excluded, primary healing without fever or other unfavorable symptoms would occur. Then followed years of arduous experimental work, in which he was hampered and harrassed, not only by professional criticism and ridicule, but by the action of the British government, which, yielding to the antivivisection clamor, enacted legislation which practically prevented his continuing this great work on English soil. Undaunted by this hostile action he transported his laboratories to France, and there, amid more favorable conditions, he completed his great work. In giving to the world a method of operating by which sepsis can be avoided, Lister's discovery must be regarded not only as the greatest contribution to surgery of this century, but as the greatest advance in surgical therapeutics of all centuries, the greatest life-saving measure of all time; for it not only removed the terrific death rate of the few operative procedures then employed, but it opened up the vast field of modern surgery, which has resulted in the relief and cure of scores of diseases, which without the aid of modern surgery led only to death, prolonged suffering, or chronic invalidism. So long as the human race suffers from injury or surgical disease, so long as surgery is practiced or taught, so long will the name of Lister be known and justly spoken of as one of the greatest benefactors of mankind.

Gentlemen, I have attempted in this informal talk to give you an idea of the standards of professional success which may be attained in addition to the gaining of a livelihood. Not that I would for a moment belittle the latter aim, for the workman in medicine is certainly worthy of his hire. But if you practice your profession ethically, with intelligence, with skill and with a large measure of human sympathy and philanthropy, you will never receive in dollars and cents anything like an equivalent of the services you render; yet it lies within the power of each one of you to attain a professional success which will be satisfying directly in proportion to your activities.

The profession you have chosen is an honorable one, its history and traditions are inspiring, its accomplishments are deserving of the greatest praise, but to succeed in it you must be prepared to give it your best efforts, your unceasing devotion, your undivided attention—you must make it in reality your life work. Remember, however, that the path to success is not an easy one: discouragement, failure, and criticism often virulent and unmerited will be your lot, if you leave the beaten track and seek to establish new principles, or advocate methods not sanctioned by tradition. Let

me urge you, however, in your periods of discouragement and trial to bear
in mind the words of the poet:

> "One ship drives east and another west,
>   While the self-same breezes blow,
> It's the set of the sails and not the gales
>   That bids them where to go.
> Like the winds of the sea are the ways of the fates,
>   As we voyage on through life;
> It's the set of the soul that determines the goal,
>   And not the storms and the strife."

<div align="right">GEORGE EMERSON BREWER.</div>

MULTIPLE INFECTIONS.*

By Mark A. Brown, M. D.

Cincinnati.

Until within comparatively recent years the presence of two or more infectious processes existing in the same individual at the same time was looked upon with a considerable degree of skepticism to say the least. Whether it was thought that because of the existence of a certain infectious disease, a particular antitoxin was introduced or generated within the body that exerted an action antagonistic to the activity of other germs, or what not, I do not presume to say. Indeed, I am not prepared to say that under certain circumstances, among certain germs or infectious processes, this antagonistic action does not take place; it opens up a field of speculation and theorizing too wide for me to attempt here. My object to-night is simply to place on record a few cases of multiple infection, cases in which there could be no doubt but that two or more infectious processes were actively at work in the same individual at the same time. In the first place, it must be assumed—and we have all of us accepted it probably long ago—that there are certain diseases which must be classed as infectious, in which no germ has as yet been isolated, that therefore do not conform to Koch's laws, but concerning which there can exist no uncertainty in the minds of those willing to accept the germ theory, but that they are dependent upon a specific organism. I, of course, refer among others to certain of the infectious diseases of childhood, to syphilis, and to the disease that brought out that most interesting paper of last Monday night—acute inflammatory rheumatism.

CASE I.
SYPHILIS AND VACCINIA.

Patient, a male, aged 28, unmarried, of good physique, well developed and nourished. He was first seen on March 16, 1900, coming to me to be vaccinated. The vaccination "took" in the usual time and began to pass through the usual changes. On the seventh day after the inoculation he came again and called my attention to an eruption that had invaded the surface of the body pretty generally, with the exception of the face. It was present to a slight degree both upon the palms of the hands and the soles of the feet. The eruption was most decidedly of a copper hue, and was not actively inflammatory in type—that is to say, the skin around each individual lesion was not at all hyperemic. It was distinctly a psoriasis, and this, combined with the marked copper color and the involvement of the hands and feet, led me to the opinion that it was syphilitic. Indeed, that was also his idea, for he freely admitted that he had had a hard chancre about

* Read before the Academy of Medicine of Cincinnati, June 2, 1902. From The Cincinnati Lancet-Clinic, October 18, 1902.

Page 6

two years previously, which had been followed by a general cutaneous eruption and later by some ulcers in the mouth. He had carried out his treatment in rather a desultory manner, but there had been no recurrence of eruption until the present time. He brought up the question, which has since puzzled me, if the vaccination could have caused a flare-up of his syphilis. The pock on his arm pursued the usual course, not severe, and scar formation took place in the usual time. At no time was there any pustular eruption present, or, indeed, any other than the psoriasis I have mentioned. He was ordered mercurial inunctions and the eruptions responded immediately, though at the end of two weeks there could still be seen very faint copper-colored stains.

CASE II.

ESTIVO-AUTUMNAL MALARIA AND PULMONARY TUBERCULOSIS.

Albert D., male, aged 25, a native of Tennessee. About two years ago he left the mountains where he had been raised and went to Texas. While there he contracted malaria of rather a severe form, which responded rather slowly to treatment. When not constantly under the influence of quinine the chills and fever would return, so that he was finally advised to return home, which he did. In all he was in Texas nine months. On returning home he improved slowly and steadily until about four months ago, when he began to lose in weight and to suffer from occasional chills, though no actual rigors. He complained mostly of weakness and of severe diarrhea, the latter often accompanied by great abdominal pain. His appetite was capricious; there were occasional attacks of vomiting. He was finally brought to Cincinnati, and I first saw him at 9:30 a. m., May 12, 1902. I mention the time of day, as on taking his temperature during the examination that followed it was found to be normal. Particularly manifest was the grave anemia, which, combined with the peculiar lemon-yellow tint of his skin, brought immediately to mind pernicious anemia; however, with the clear history of malaria given, this opinion was not long entertained, though there is no reason why the two could not exist together, some authorities, indeed, giving malaria as one of the causes of pernicious anemia. The temperature, as has been said, was normal; the pulse about 100, of low tension and markedly dicrotic; as indications of the anemia, the feet and ankles were markedly edematous. The lungs were not examined at that time, as there was absolutely no history that would lead one to believe that they were involved. A superficial examination of the heart revealed a slight systolic murmur, which was ascribed to the anemia. He was sent at once to the Presbyterian Hospital, with orders as to treatment.

As I had to leave the city that afternoon I did not see him until the morning of the 14th, when the first blood examination was made. The blood when drawn from the ear showed little tendency to coagulate. Examination of the fresh unstained blood showed the plasmodium of Laveran after about five minutes' search. The first three specimens were quite small, rounded,

with most of the pigment at the periphera, no portion of red corpuscle remaining. The pigment granules were small, but such as were toward the center showed movement, though sluggish. The fourth specimen was an egg-shaped corpuscle with one pole occupied by the parasite, in which latter movement of the pigment granules was distinctly visible. Dr. Oliver and the internes who afterwards examined the slide told me that they had found crescents, which were what I myself had been particularly in search of. There was no poikilocytosis. There was some free pigments in the blood and the few leucocytes seen were markedly pigmented.

The diagnosis of estivo-autumnal malaria was made and quinine ordered; the slight effect of the latter treatment can be seen by the most casual inspection of the temperature chart. It will also be noted from the temperature chart that the rise always began about noon and continued throughout the afternoon and evening—hectic, indeed; while in malaria it has been my experience to have the paroxysm in the morning, though of course this is not always the case. I was satisfied that estivo-autumnal malaria was present in this case, and malaria of this nature is usually accompanied by a mild continued or slightly remittent fever, or in chronic cases, in which few organisms are present, as in the one under consideration, by no fever at all. In this case, too, the rise of temperature was never accompanied by chills. Lastly, there was the total failure of response to quinine; I have always believed the dictum that any intermittent fever which does not in three or four days respond to quinine is not malarial. I knew positively that estivo-
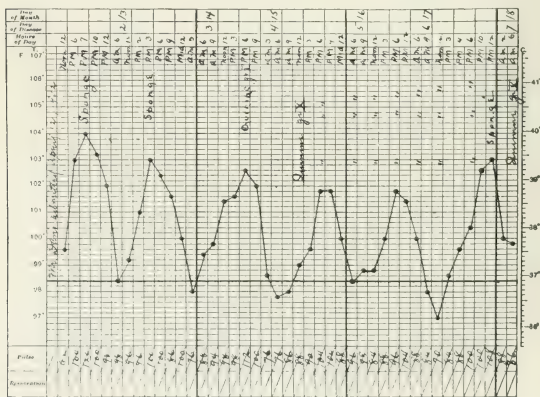
Estivo-autumnal malaria and pulmonary tuberculosis (Case II)

Fig. 60

autumnal malaria was present—the typical specimens showed that—though it was rather unusual to find the regular intra-corpuscular parasites and the crescents in the same peripheral field; then, too, as indicated before, one would not expect from the examination of the blood a fever of the type here shown. The natural conclusion was that there was another lesion present that had been overlooked. It was not hard to find; examination of the left apex of the lung revealed dullness, and immediately under the clavicle, at about its center, was well-marked cavernous breathing. The cavity was quite small. A few mucous râles were present over the left lung, extending to about the fourth rib. Posteriorly these rles could be heard extending to the upper level of the infra-scapular fossæ. That was all, surely not enough to account for the great loss of weight—about 60 pounds—and strength, and the profound anemia (the blood count was about 2,800,000), all within the space of not over four months. On questioning the nurses in charge, it was learned that he had coughed but rarely, and expectoration, on reference to his spit-cup, occurred but four or five times in the twenty-four hours. He himself was so little annoyed by these latter symptoms that he had not thought it worth while to mention them to me. The examination of the sputum revealed tubercle bacilli in large numbers, as well as an abundance of the germs of suppuration. The examination of the urine was entirely negative. The stools were, as a rule, loose, sometimes of a greenish color, and often containing mucous. The liver was markedly enlarged, the spleen less so.

It seems to me, in the explanation of this case, that the lessened vitality caused by the invasion of the plasmodium so lowered his resisting power that he was unable to withstand the onslaught of the tubercle bacillus, even though assisted by a pure mountain air, good hygienic surroundings, and the best of good country food.

This case has been of particular interest to me in view of the fact that every year probably thousands of cases of early phthisis are called malaria; the combination of the two diseases in the same individual is, I believe, a little unusual, at least it is the first case of the kind that has been brought to my attention. I do not believe, in view of the absence of response of fever to quinine and the few parasites found, that the fever was in any way dependent upon the malarial infection; the chart shows it to be a typical example of that fever occurring during the first few months of phthisis, the so-called fever of tuberculization. I might say, in conclusion, that after a week's use of the quinine the parasites could no longer be found in the peripheral blood and the size of the spleen was markedly reduced.

CASE III.
WHOOPING COUGH, ACUTE INFLAMMATORY RHEUMATISM, LOBAR PNEUMONIA.

The previous history in this case is of some importance. The older brother of my patient is aged 25, is married, and lives in Newport, Ky. He

came to my office February 13, 1902, suffering from acute follicular tonsillitis. He thought that there might be some diphtheria connected with his case, so, afraid of infecting his infant son, he determined to go to his mother's home in Cincinnati. He was well in a few days, but about a week after I first saw him, a younger brother, aged 14, also living with the mother, was taken down with a similar trouble, and in another week the youngest brother, aged 8. On April 3 I was called to see the fourteen-year-old boy, Frank, and found him suffering from acute inflammatory rheumatism affecting the right ankle; next day it had moved over to the left. Under combined salicylate and alkaline treatment he rapidly convalesced without cardiac lesion or involvement of other joints.

On April 6 I was asked to see H. S., the eight-year-old child and the subject of the present report. He was suffering from a mild fever and rather a severe cough, not in any way spasmodic, while on physical examination there was but a mild bronchitis present. On April 12 the fever rose rapidly and he complained of severe pain in the right ankle and shoulder. Examination showed the shoulder to be exceedingly painful and tender, though I could detect no swelling; the ankle, however, showed all the evidences of an acute inflammation. The next day the other ankle was involved, the disease then transferring itself to the wrists and fingers. He also responded to the combined treatment. On April 14 the cough became distinctly paroxysmal, the child having about eighteen to twenty attacks in the twenty-four hours; the attacks occurred mostly at night and in the early morning hours, and ended in the typical whoop. I heard him in several of his paroxysms, and there could be no doubt as to the existence of whooping-cough. Belladonna was given and pushed to dilatation of the pupils, with the results so far as lessening the number and severity of the attacks was concerned. On April 30 another rise of temperature supervened, soon followed by dullness and bronchial breathing in the lower right lung. The examination of the sputum revealed the diplococcus of Fraenkel. Crisis occurred on the fifth day of the disease, and convalescence from his triple infection proceeded rapidly. I have seen both of the younger children since their recovery on several occasions, and as yet there is not the slightest evidence of any cardiac involvement.

This case has interested me because of the apparent casual relation existing between the tonsillitis and the inflammatory rheumatism; I have observed this relation often, though perhaps never in so satisfactory manner as in the present case. Osler, in speaking of the relations of pneumonia and rheumatism, makes the following statements: "The arthritis may precede the onset, and the pneumonia, possibly with endocarditis and pleurisy, may occur as a complication of the rheumatism. In other instances, at the height of an ordinary pneumonia, one or two joints may become red and sore. On the other hand, after the crisis has occurred pains and swelling may come on in the joints."

CASE IV.
TYPHOID FEVER AND SINGLE TERTIAN MALARIA.

The term typho-malarial fever has been in common use in medical litera-
ture for many years, and even at present one occasionally encounters it. It
was supposed in past years that there occurred a combination of the typhoid
and malarial poisons—a community of interests or trusts, as it were—and
that this new combine manifested itself in "ways that are dark and tricks
that are vain," however, to the complete baffling of the common people,
i. e., the physician. The latter, however, boldly came to the front and an-
nounced with pride that the new combine manufactured a product that,
when poured out into the system, caused a continued fever with marked
remissions which was extremely resistant to quinine. This was satisfactory
to all concerned with the exception of the poor patients, who didn't count,
as they always have to suffer in the cause of science, anyway, so they were
deluged with quinine until their ears rang and rang again and they were
deaf to their own entreaties. Laveran's discovery of the plasmodium
malariæ straightened matters considerably, and the introduction of the agglu-
tination test of Pfeiffer-Widal completed the route of the Typho-Malaria
Trust. Chills, with the added phenomena of heightened fever and sweats,
are not at all uncommon at any stage of typhoid fever. The disease may be
ushered in with a chill, though this is rare. During the course of the disease
chills may be the premonition of some such complication as pneumonia,
pleurisy, otitis, periostitis or perforation; or they may follow a too vigorous
use of coal-tar derivatives, particular guaiacol locally applied to the abdo-
men. During convalescence—and these are the cases to which the term
typho-malaria is so often misapplied—they may occur bearing no relation
to the above-mentioned causes, but from reasons not entirely understood,
though probably dependent upon septic infection or autointoxication, as
when the bowels have been allowed to remain confined for several days.
However, a coincident infection with the malarial parasite may occur at
any time during the typhoid attack, though it is rare, and a positive diag-
nosis must not be made without finding the plasmodium in the blood. In
most cases there has been a previous malarial attack, and the flare-up of
the latter occurs during the typhoid convalescence.

P. K., Jr., aged 24, a native of Cincinnati, and has lived in this neigh-
borhood all his life. Was first seen on May 10, 1900. Previous history
negative, aside from the ordinary diseases of childhood and an attack of
chills and fever a year ago, which had promptly responded to quinine.
When I first saw him he had been sick about a week with the usual initial
symptoms of typhoid fever, including the nose-bleed. In a few days the
spleen could be palpated and rose-spots developed upon the abdomen. The
Widal reaction, made several times, was positive. The attack was quite a
mild one and was unaccompanied by chills until convalescence was well
established. Indeed, the attack was so light that it was not found necessary

to adopt any antipyretic measures, though the temperature did on several occasions exceed 103 degrees. (I have found that among people of ordinary intelligence a fairly reliable temperature record can be kept, which can, if found necessary, be subsequently charted; and I have made it a rule in fevers to appoint some reliable member of the family to take the temperature regularly, as was fortunately done in this case.) When the evening temperature approached the normal, visits were made late in the afternoon, so that the evening temperature at least could be verified. On the evening of May 28, convalescence having been well established, the temperature was found to be 101.8 degrees. The mother told me that the boy had had a slight chill at ten that morning, and that his temperature had gone to 103.8 degrees by noon. He had then broken out into a sweat, and by 3:00 p. m. the fever had dropped to 102.6 degrees. The next morning the temperature was normal, and I obtained a fresh specimen of blood, which was found to contain an abundance of half-grown tertian malarial parasites. He had no chill that day, and the evening temperature was but 99.2 degrees. He was ordered ten grains of the bisulphate of quinine, to be given at eight the following morning. The chill occurred at about 10:15 a. m., the temperature going to 103.4 degrees by noon. Quinine bisulphate was then ordered in four-grain doses three times a day, with a resulting disappearance of the malaria. As said before, the typhoid had about run its course, so that the patient was soon able to be discharged. He has had one attack of malaria since that time.

In this case there was a coincident typhoid and malaria infection. The diagnosis of typhoid was made by the history, the enlarged spleen, the character of the fever, the rose spots and the Widal reaction. The diagnosis of single tertian malaria was made by the occurrence of morning chills and rigors every third day, the finding of typical tertian organisms in the blood and the therapeutic test.

DISINFECTION OF THE KNEE JOINT.*

ROBERT B. COFIELD, M. D.

Cincinnati.

Whether in civil or military practice, it is generally conceded that septic infection of the knee joint is one of the most serious conditions that the surgeon can be called on to treat, endangering, as it does, both the future usefulness of the joint, and at times, the very life of the individual.

In civil experience we have formerly been led to a profound distrust of the ability of this particular articulation to deal with infective processes. In septic arthritis, an arthrotomy was usually advised and drainage tubes or wicks were inserted into the joint cavity, or through and through drainage was established and the tubes allowed to remain for at least a number of days. Besides producing an evil mechanical effect on the synovia and cartilages, the drainage material provided an ideal reservoir for the pabulum in which the organisms could multiply and travel from within outward, spreading infection to the para-articular structures, or from without inward, carrying secondary infection from the skin into the joint cavity.

The anatomic structure of the knee joint is such that when it is severely infected over its whole extent, drainage becomes a serious and difficult matter, and even though skilfully done, it is a most unsatisfactory procedure, often resulting in the tracking of the infection along the muscular and fascial planes, above or below the joint, with the accompanying dangers of septicopyemia and severe damage to the joint structures, resulting in ankylosis.

CONDITIONS NECESSARY FOR FAVORABLE RESULTS.

The results achieved in the present war, in treating infected wounds of the knee by disinfection and immediate closure, have been the source of much surprise and satisfaction. Favorable results, however, with restoration of joint function, seem to depend on the observance of certain principles which are doubtless of equal importance in treating septic arthritis of autogenous origin:

1. The operation must be done early, before the spread of infection and the disorganization of the joint structures have had time to occur.

2. Thorough lavage of the infected and contaminated areas, followed by primary closure of the joint capsule, is essential.

3. Foreign bodies must not be allowed to remain within the joint cavity.

4. When drainage is used at all, it should be carried down to the capsule, but not into the joint cavity.

5. Immobilization of the joint must be secured by adequate mechanical fixation.

In order for a surgeon to carry out these principles effectually, it is of the utmost importance that a diagnosis of suppurative arthritis be made early in the course of infection. This is not often difficult, since the joint involvement usually accompanies or follows a focal or general infection, originating elsewhere in the body, such as, gonorrhea, tonsillitis, otitis media, scarlet fever, pneumonia, etc.

This form of arthritis may be secondary to a serous synovitis or it may start without any obvious serous stage. The septic joint is often ushered in with a chill, the temperature is elevated, the capsule becomes distended with fluid, and the joint is inflamed and painful and is held in a semiflexed position by the spasmodically contracted muscles.

Every joint that shows evidence of inflammation and effusion, during the course of a focal or general infection or following it should be aspirated under strictly aseptic precautions for diagnostic purposes. The nature of the aspirated fluid will be a very definite guide as to the proper course to pursue.

The bacteriologic side of the investigation so often fails to reveal the presence of micro-organisms in the joint fluid, either in smears or cultures, that considered by itself, it carries little weight, and negative findings in this regard should not influence the course of our treatment.

The cytologic investigation of the joint fluid, however, is a distinct aid to the diagnosis, and at times will materially influence the prognosis, in joint effusions. A high percentage of polymorphonuclear leukocytes found in a sample of the aspirated fluid will afford positive evidence of a septic condition. The normal synovial fluid from the knee joint is acellular. Pus, which consists of practically 100 per cent. polymorphonuclear leukocytes, is a surgically visible sign that infection of the part has occurred and calls for prompt surgical intervention.

TECHNIC OF DISINFECTION.

The technic which I have followed in disinfecting the knee joint is briefly as follows:

The knee joint is prepared the day previous to operation by being shaved and scrubbed and wrapped in sterile dressings. After the patient is anesthetized, the field of operation is further sterilized with benzin and iodin. An incision 1½ or 2 inches long is made parallel to the inner or outer border of the patella, extending into the joint cavity. If found desirable this incision may be extended to facilitate a more complete exploration of the joint. By means of a gravity syringe, placed high enough to give the stream considerable pressure, the joint cavity is now thoroughly flushed for fifteen or twenty minutes. Instead of using the sterile glass tip, commonly attached to the tubing leading from the container, it is better for the operator to use a soft rubber tip which may be inserted into the various recesses of the joint without the danger of injuring their delicate lining.

Various solutions have been used with success for disinfection of septic joints. Some operators even assert that the results do not depend on the

nature of the solution employed, but rather that it is the thorough mechanical cleansing which is the important factor. However, since it has been shown that the synovia and cartilage withstand very well the active disinfecting agents, and since the pathogenic organisms are harbored within the synovia and para-articular tissues, and not in the joint cavity, I prefer to use an active disinfectant which possesses a penetrating as well as a cleansing action. Mercuric chlorid, 1 : 15,000, in salt solution, as suggested by Dr. Cotton of Boston, maintained at a temperature of about 115 F. and this followed by physiologic sodium chlorid solution, has proved very satisfactory.

Since the capacity of the synovial cavity of the knee joint reaches its maximum when the leg is flexed to an angle of about 25 degrees, and since the contents of some of the bursae communicating with the joint are most easily emptied when the limb is in a semi-flexed position, it is very important that flexion and extension of the joint should be passively carried out while the cavity is being flushed. This will aid materially in ridding the joint of the necrotic material and pus that have accumulated in these various pouches. It is also advisable repeatedly to press the edges of the wound close about the tip of the syringe in order that the fluid may distend the joint capsule and penetrate and flush out its various recesses.

The objects sought by arthrotomy and irrigation of the joint cavity are:

1. Relief of the intra-articular tension, which doubtless has a deleterious effect on the synovial membrane and cartilages through its interference with the circulation and the normal secretory function of the synovia.

2. The removal of the necrotic material which acts as a culture medium within the joint cavity. The nature of this material precludes its removal by means of the trocar or an aspirating syringe.

3. The cleansing and disinfecting action on the synovia, which aids it materially in regaining a normal function and renewing its fight against infection. The synovial membrane, like other serous membranes, has an enormous capacity for combating infection if it is a fairly normal condition.

After disinfection, the capsule is closed with catgut sutures, and if a drain is used at all, it is placed outside the synovial membrane for the sole purpose of taking care of the extracapsular infection. The wound is closed in layers and the joint is thoroughly immobilized, preferably by a plaster-of-Paris spica including the foot.

A fenestra may be cut over the knee and if an increase in the inflammation and effusion should occur, aspiration may be repeated, depending on the nature of the fluid as to the future course of procedure. It is not frequent, however, that any further difficulty is encountered. The temperature and pain usually subside within a few days, and the joint gradually resumes a normal condition.

POSTOPERATIVE MEASURES.

The limb is maintained in a position of physiologic rest until the wound is entirely healed and all signs of inflammation have disappeared. The

patient is then given the privilege of active motion once or twice a day, depending on the sense of pain as a guide to the extent of movement. Later, gentle passive motion, along with heat and massage, will often hasten recovery, but at first the utmost gentleness is necessary in order to minimize the risk of exciting a recrudescence. The absence of signs of inflammation does not always assure the absence of pathogenic organisms, and well meant efforts to establish mobility may set up an active condition within the joint, if passive motion is applied too vigorously or begun too soon.

Should fibrous adhesions form, which we feel reasonably sure are peri-articular, they may be broken down by forced manipulations, with the patient under full anesthesia, in order to secure complete muscular relaxation, thus permitting the movements to be carried sufficiently far in all directions.

Intra-articular adhesions are best treated by gradual correction by means of suitable mechanical appliance, since rough handling is followed by further damage to the joint structures and still greater limitation of movement within the articulation.

THE MECHANISM OF SHOCK AND EXHAUSTION.*

By George W. Crile, M. D., F. A. C. S.

Cleveland.

The man in acute shock or exhaustion is able to see danger, but lacks the normal muscular power to escape from it; his temperature may be subnormal, but he lacks the normal power to create heat; he understands words, but lacks the normal power of response. In other words, he is unable to transform potential into kinetic energy in the form of heat, motion, and mental action, despite the fact that his vital organs are anatomically intact. His mental power fades to unconsciousness; his ability to create body heat is diminished until he approaches the state of the cold-blooded animal; the weakness of the voluntary muscles finally approaches that of sleep or anesthesia; the blood-pressure falls to zero; most of the organs and tissues of the body lose their function.

It is evident, therefore, that in exhaustion the organism has lost its self-mastery. Self-mastery is achieved only by the normal action of the master tissue—the brain. In exhaustion, then, is the brain primarily exhausted; or has some other tissue or organ functionally broken down, and has that breakdown carried with it exhaustion of the brain? If the latter, then what organs and tissues are vitally necessary to the brain for the performance of its function? Obviously, the exhaustion of any organ or tissue not vital to the performance of brain function need not be considered, since it probably would not be a direct cause of acute exhaustion.

I. TISSUES AND ORGANS WHICH BEAR NO IMMEDIATE RELATION TO THE PROBLEM OF ACUTE EXHAUSTION.

Among the tissues and organs that are not immediately vital to the brain, within the period of death from *acute* exhaustion, are the bones and joints, the connective tissue, the neutral fats, the skin, the genito-urinary system, the digestive system, the gall-bladder and ducts, the lymphatic vessels and glands, the salivary glands, the spleen, the sweat glands, the pancreas, the thyroid, the thymus, the organs of common sensation, the nails, the hair. Want of activity of any of these organs or tissues individually or collectively cannot produce acute exhaustion in the sense in which that word is here used. That is to say, a man in exhaustion from the injury and the struggle of battle would not be restored if he were given rested eyes, rested ears, rested sweat glands, rested spleen, rested genito-urinary system, rested digestive system, rested bones and joints, rested connective tissue, rested skin, rested gall-bladder, rested fat.

II. TISSUES AND ORGANS WHOSE FAILURE OF FUNCTION MAY PRODUCE ACUTE EXHAUSTION.

The tissues and organs, whose failure of function may cause acute exhaustion, are the respiratory system, the circulatory system, the blood, the muscles, the adrenals, the liver, and the brain.

*From Journal A. M. A., November 23, 1920.

Page 75

RELATION OF THE RESPIRATORY SYSTEM TO SHOCK AND EXHAUSTION.

The failure of the respiratory system to deliver sufficient oxygen to the blood or to take sufficient CO_2 from the blood, exhausts and kills promptly. Failure of the respiratory system is not a universal, not even a common cause of exhaustion, for in the great majority of cases of exhaustion, the respiratory activity is even increased and there is no interference in the lungs with the exchange of gases. The interference with the pulmonary mechanism of air exchange that may cause exhaustion is most commonly produced by edema of the alveolar walls; by pulmonary embolism; by the exudations of pneumonia; by fat embolism; by the inhalation of water, or of pus, or of free blood; by excessive pleural effusion; by emphysema; by hemo- and pneumo-thorax. In each of these conditions, there is interference with the intake of oxygen and the elimination of carbon dioxid which may be sufficient to cause exhaustion and death.

THEORIES REGARDING THE RELATION OF THE RESPIRATORY SYSTEM TO SHOCK AND EXHAUSTION.

Fat Embolism Theory. Roswell Park first suggested and Bissel demonstrated the presence of fat embolism in the lungs of patients who were diagnosed as being in surgical shock. Porter has extended Bissel's observations into an inclusive theory of shock. He concludes that shock is due mainly to diffuse fatty embolism of the lungs. There are several facts that apparently are not harmonized by the fat embolism theory.

(a) In cases of abdominal penetration, if there is no perforation of the hollow viscera and no hemorrhage, there is little shock; if there is either perforation or hemorrhage, or both, there is shock. Since, in either case, the same fat areas have been traversed, it follows that the traversing of the fat was not the determining factor.

(b) In emotional shock, so common in battle, it is difficult to assign to fat emboli a causative role.

(c) In shock from burns, the difficulty is no less.

(d) In shock from chest and head injuries, it is almost as difficult to assign a causative role to fat emboli. Many other examples may be cited.

On the other hand, surgical literature contains many accounts of the presence of fat emboli in fracture cases—especially fractures of the long bones, and these cases show no shock at first, but later develop a train of symptoms resembling shock.

Wiggers performed a series of experiments to determine whether the mechanism which causes failure of the circulation after the intravenous injection of oil is the same as that which causes circulatory failure in surgical shock. He concluded that circulatory failure produced by fat emboli must be distinguished from circulatory failure due to surgical shock. The

conclusions of Wiggers are in more complete accord with surgical experience than those of Porter. With respect to the CO_2 treatment which Porter proposes, on the theory that the increased action of the diaphragm caused by the CO_2 would force the fat emboli out of the capillaries into the free circulation, it would obviously be difficult to determine how much of the clinical result might be due to pooling of the blood in the abdominal veins, for which Porter advises CO_2 inhalation, and how much to pulmonary fat embolism for which also he advises CO_2 inhalation. That is, would the clinical result be due to the pumping of the blood out of the abdominal vessels by the increased respiration induced by the inhalation of CO_2, or to the driving of the fat out of the lungs, or would it be due to the relief of acapnia (Henderson)? But since in practice the CO_2 treatment has yielded no advantage to the patient, this point will not be pursued further.

Henderson's Acapnia Theory. Yandell Henderson has plausibly advocated the view that excessive ventilation of the lungs—resulting in excessive elimination of CO_2 from the blood—is the cause of shock. Since the respiratory center is controlled largely by the CO_2 tension of the blood, it follows that in shock the respiratory exchange would be diminished, so that, as Henderson believes, there would result a state which is below the point of oxygen safety.

Henderson's theory is one which every surgeon would hope might be true, for apparently it would make both the prevention and the cure of shock easy and simple. There are many arguments in favor of this theory. The disturbing effect of excessive ventilation of the lungs is apparent. It is true that oxygen improves the condition of the patient in shock, that lack of oxygen leads to acidosis. Nevertheless there are certain difficulties in the way of accepting fully Henderson's conclusions.

(a) As we have stated above, the clinical use of CO_2 in shock has not proven to be of much value. It is possible that this is because serious intracellular damage has been inflicted upon certain vital organs before the CO_2 treatment was begun.

(b) In my laboratory, animals under curare and continuous adequate and even artificial respiration—thus eliminating the excessive ventilation (acapnia) factor—could still be killed by shock from trauma.

(c) Protracted consciousness—insomnia—in animals, subjected to no other excitement, causes complete exhaustion. Acapnia could scarcely be a factor here. It should be added that Henderson has not discussed this type of exhaustion.

CONCLUSION.

In exhaustion from running, from fevers, from trauma, from anesthesia, from excision of the liver, from excision of the adrenals, from hemorrhage, from emotion, from insomnia, the exhaustion is not in any way related to the lungs. If there is a coexistent defect in the pulmonary function, by so much the more readily is exhaustion produced by trauma; by emotion, by

fever, by exertion, by hemorrhage, etc. We, therefore, conclude that the primary cause of exhaustion may be found in the *pulmonary system, but that this is not a common primary cause.*

CIRCULATORY SYSTEM.

Failure of the circulation exhausts and kills inevitably, and failure of the circulation is established sooner or later in acute cases of grave or fatal exhaustion. The question therefore is: Is the failure of the circulation a primary or a secondary cause of exhaustion, or is the circulatory factor sometimes a primary and sometimes a secondary cause of exhaustion?

THE HEART.

The heart may be unable to pump the blood stream forcibly enough to maintain adequate circulation, in which case general exhaustion will occur as the result of lack of oxidation of the tissues. Exhaustion occurs clinically in the myocarditis of acute or prolonged infections; as the result of excessive muscular exertion; in anemia; in the presence of valvular defects. But observations in both the clinic and the laboratory show that in surgical shock and exhaustion, the heart muscle has not failed.

DISTRIBUTION OF BLOOD.

Pooling in the larger veins. A number of observers have held the view that in shock the blood accumulates in various blood-vessels, this pooling becoming in effect an intravascular hemorrhage. There are certain facts, however, which are not harmonized by this theory.

(a) In the author's laboratory, experiments showed that shock could be produced in animals in which the abdominal vessels or the thoracic aorta had been excluded by ligation, though not quite as readily as in the controls. Erlanger and others have shown that excision of all the abdominal viscera does not lessen the liability to shock. In our experiments we found also that if the intestines were so tensely distended with water as to drive out all the blood, then trauma of the peritoneum no longer caused a primary fall in blood-pressure, but death from shock might occur. Many dissections before death, many autopsies after death from trauma to other parts of the body than the abdomen, showed that the blood was held in the veins everywhere, as in death from other causes.

(b) As stated in a preceding paragraph, Porter has proposed the inhalation of CO_2 for the purpose of increasing activity of the diaphragm, to the end that the supposed accumulation of blood in the abdomen would thus be put into more active circulation. No clinical advantage from this treatment has been reported.

(c) Treatment with intraperitoneal injections of pituitrin, as suggested by Cannon, even more effectively facilitates the splanchnic venous circulation than does Porter's CO_2 inhalation, but this method has not proved to be a cure for shock.

From the evidence in hand, we are not warranted in concluding either that blood does or that it does not pool. We only infer that even if it does pool, this is an end effect—not a primary cause of shock.

Accumulation of the Blood in the Capillaries. Cannon has advanced strong arguments in favor of the view that the small blood-vessels—the capillaries—are dilated, and in dilating have engulfed so much of the volume of the blood as to seriously interfere with the circulation. If this were true, then the universal bandaging of the body alone, or blood transfusion alone, or bandaging and blood transfusion combined, should both prevent and cure shock. But both laboratory and clinical experience show that, although these measures are useful, they are not specific.

VASO-MOTOR MECHANISM.

Is the vaso-motor mechanism a factor in shock? In 1897 the theory that shock was due to the impairment or breakdown of the vaso-motor mechanism was proposed by the writer. Owing to the fact that control of the blood-pressure did not specifically cure shock it soon became obvious that exhaustion and shock included much in addition to the failure of the vaso-motor mechanism.

Opposing views as to the state of the vaso-motor mechanism have been presented by various investigators.

(a) Seelig and Lyon have concluded that the vaso-motor mechanism is functionally intact in shock.

(b) Porter has found that vaso-motor stimulation produces a progressively diminished rise in blood-pressure as shock deepens. This finding is in accord with our own data. Porter has interpreted the blood-pressure change on the basis of a percentile rise, and has concluded that the vaso-motor mechanism is not altered in shock. It is open to question, however, whether Porter has not proved the opposite of his conclusions, for if, in shock, adrenalin be given intravenously, or pressure on a paw be made, the percentile rise interpretation will be reversed. Applying Porter's percentile interpretation to the effect of adrenalin the percentile rise would be over 300 per cent., that is, according to Porter's reasoning, the vascular state is three times better than normal, but nevertheless, the dog is dying. The error in Porter's reasoning may be made more clear by a homely illustration. If a goad be applied to a fresh horse, the resulting increase in speed may be stated as a percentile increase. When the horse is in extreme fatigue and an equal goad is applied, the percentile increase will probably be the same, but nevertheless the horse is exhausted.

(c) Erlanger and his associates found that the vaso-motor mechanism is exhausted late in shock. They suggest that the primary fall in blood-pressure may be brought about by the effect of painful stimuli and hemorrhage.

(d) Pike and Coombs believe that damages to the brain-cells must be included as one of the conditions of traumatic shock.

(c) Wiggers observed a steady fall in vaso-motor tone in the early phases of shock. He concluded that the peripheral resistance was diminished, indicating diminished vaso-motor tone.

Our experimental data show that there is no practical distinction to be made between external stimulation of the vaso-motor center as in injury and operation, and internal stimulation by vaso-motor stimulants, as strychnin. Each in sufficient amount produces exhaustion (shock), and each with logic might be used to treat the shock produced by the other. We conclude, therefore, that in traumatic shock the vaso-motor mechanism is functionally impaired or exhausted.

Experience in the clinic, however, seems to show that, whereas in shock the depression and fatigue of the vaso-motor centers were very important, there must also be other important effects. This was all the more probable because of the time required for recovery; the long after-effects; the inadequacy of merely raising the blood-pressure; the weakness and debility of the injured animal before a fall in blood-pressure had occurred; the facts that infection, loss of sleep, hunger and thirst predisposed to exhaustion and that ether anesthesia predisposed to exhaustion. All these clinical observations demanded renewed research. The work of Hodge on fatigue in bees and birds suggested such an investigation. To that end the studies of the brain cells, which have been summarized in former publications, were undertaken. These studies immediately gave us illuminating results. Our argument was that if the vaso-motor center was fatigued in shock and exhaustion, other parts of the brain were probably fatigued also. If the brain cells were functionally altered, one would expect them to be physically altered, as Hodge had shown was the case in his studies of fatigue in the bee. We argued that in shock not only are the vaso-motor cells exhausted, but the cells of the brain that preside over voluntary muscular action and mental action are also altered; in other words, that the brain as a whole is altered, and is altered independently of, as well as in consequence of, the low blood-pressure due to the exhaustion of the vaso-motor centers; that the higher centers may well be affected even more than the vaso-motor

The vaso-motor mechanism alone, the blood-pressure alone, is not sufficient to account for all the phenomena of shock; and although some of the causes of exhaustion may be found in the respiratory system, and some in the circulatory system, we must look elsewhere for the explanation of the vast majority of cases of shock and exhaustion. Are these due to some change in the blood?

THE BLOOD.

Chemical Changes in the Blood. The blood is a vital fluid for all the tissues. If there is insufficient blood, or if the blood is sufficiently impure, exhaustion of every organ and tissue will follow. The acute exhaustion caused by hemorrhage is cured in a normal animal by immediate replace-

ment of the lost blood by an equal amount of good blood from another animal. If impure blood is the primary cause of exhaustion, and no other primary cause exists, then the removal of impure blood and the substitution of pure blood should bring relief from exhaustion in proportion to the amount of impure blood exchanged for pure blood. If exhaustion is due to some change in the blood, then if an acutely exhausted animal had its blood withdrawn as completely as possible and normal blood replaced, the same process being repeated several times so as to be certain that a sufficient amount of blood had been exchanged, demonstrable relief should follow. But experiments have shown that not many cases of exhaustion may thus be benefited or cured. Moreover, animals exhausted by insomnia show no change in the blood picture, as has been shown by our experiments. We have found, also, that in patients in whom exhaustion has developed gradually, there may be no change in the blood.

The common pathologic change in the blood in acute exhaustion is acidosis. If this were the primary cause of exhaustion, then infusion of sodium bicarbonate should prevent and cure; but both laboratory and clinical evidence shows that alkalies neither prevent nor cure shock.

Cannon has found decreased reserve alkalinity in wounded soldiers in shock. He found this decrease was more marked in operation under ether than in operations under nitrous oxid; he believes that a diastolic blood-pressure of about 80 is a critical level at which acidosis rapidly develops. These phenomena are obviously secondary causes of exhaustion.

Cannon, Dale and Bayliss have recently found that the pulpefaction of muscles causes a fall in blood-pressure when the nerve supply of the injured part in blocked; and that this is prevented when the circulation of the part is blocked. Even so, macerated muscle products could be but a minor factor in the production of shock, for (a) tourniquets minimize shock only as far as they minimize hemorrhage; (b) spinal and local anesthesia almost specifically prevent shock; (c) many causes of shock, such as abdominal operations, joint injuries, skin injuries, etc., have no relation to muscle poison; (d) nitrous oxid anesthesia is all but a preventive of shock. How can these facts be reconciled with the view that the cause of shock is low blood-pressure, the low blood-pressure in turn being caused by muscle poisons? Even if under exceptional circumstances the presence of muscle toxins constituted a causative factor, their shock-producing value would be identical with that of toxemia from any other cause.

Concentration of the Blood. The blood volume is apparently diminished in shock. Has the plasma left the vessels and gone into the tissues? If so, is the process an adaptation or is it a pathologic effect? This point was investigated in our laboratory by Drs. F. W. Hitchings, A. N. Eisenbrey, and C. H. Lenhart, who found that in shock the concentration of the blood was increased up to 20 per cent., but other considerations made it obvious that this is not a primary cause of shock.

"In the blood of the 'shock dogs' there was an increase in the number of the red cells per cubic millimetre while in the blood of the 'hemorrhage dogs' there was a decrease in the number of red cells per cubic millimetre.

. . . . .

"In the 'shock dogs' there was a decrease in the number of white corpuscles while in the 'hemorrhage dogs' there was a preliminary decrease followed by a marked increase."*

Mann performed a more extensive research along the same line, and attributed greater importance to the increased concentration. Cannon has shown further evidence of loss of plasma in shock, and supports Mann's estimation of the value of this data rather than our own. Now, if increased concentration were the cause of the small amount of blood, if circulatory failure were due to a 'plasma hemorrhage' into the tissues, then adequate transfusion of blood should prevent and cure shock, but adequate transfusion of blood is not a specific cure. In addition, on this theory, the careful work of Hogan and Bayliss on the infusion of colloidal solutions, should have given us a cure, because it is known that these solutions do not leave the blood stream. But colloidal solutions fail to hold the blood-pressure—fail to cure advanced cases. The transference of plasma is probably an adaptive protection.

Then, again, even granting that the blood contains impurities which cause exhaustion, where did the blood get those impurities? From the cells. And the cells? From their increased metabolism. What caused that increased metabolism? Certain of the excitants of exhaustion. We conclude, therefore, that in the absence of primary disease—causing changes in the blood, and in the absence of hemorrhage, changes in the blood or in the blood-pressure are a *secondary*, not a primary cause of exhaustion.

VOLUNTARY MUSCLES.

If the voluntary system were exhausted primarily in shock, then there would be prostration, low temperature, lowered blood-pressure, but not the extremely low blood-pressure often seen in shock, no sweating, no loss of mental symptoms. Therefore, it at once becomes apparent that primary exhaustion of the voluntary muscles could not be adequate cause of *all* symptoms of exhaustion.

Is exhaustion of the voluntary muscles the cause of the lowered body temperature? Is the inability of the muscles to act due to a primary change in the muscles, while the brain is normal? This seems improbable, for the following reasons:

(a) The voluntary muscle is more resistant—more than fifty times as resistant—to low blood-pressure and anemia as the brain. (Crile-Dolley.)

(b) The muscles in the acutely exhausted subject show no histological

change. They can be made to contract by electric stimulation of their nerve supply, or by electric stimulation of the muscle directly.

(c) It is a physiologic axiom that voluntary muscles are not as readily exhausted as are the nerve centers that govern them.

(d) If there is primary exhaustion of the muscles, then, according to Bayliss, it would probably be due to the over-production of acid or other injuring by-products as a result of injury or work performed. But in exhaustion from trauma under anesthesia, the muscles have done no work; in exhaustion from fear, the muscles have done little work; in exhaustion from overwhelming toxemia, there has been no muscular work. Finally, we know that in a vast number of the injuries which cause shock, no muscle is involved, *e. g.*, injury of the skin, brain, knee-joint, hands or feet may result in shock.

We must, therefore, conclude that the voluntary muscular system plays a secondary, not a primary role in exhaustion. We have seen that the respiratory and the circulatory systems and the voluntary muscular system are sometimes primary causes of exhaustion, and frequently secondary causes. We have seen that in exhaustion all these tissues suffer a variable amount of disability, but the primary common cause of shock remains to be disclosed.

THE ADRENALS.

The criteria for the objective study of the adrenals are the adrenalin output, the electric conductivity, and the histologic picture. Elliott, Cannon, and others have found an increased adrenalin output and a diminished adrenalin content in certain cases of exhaustion, *e. g.*, in exhaustion due to inhalation anesthesia, to infections, and to emotion. Short found no notable diminution in the adrenalin content in shock; Bedford found no diminution of adrenalin output in shock; Mann disassociates the adrenals from shock. In our laboratory we found cytologic changes in the adrenals in exhaustion from any cause, including insomnia, these changes being more marked in the cortex than in the medulla.

THE RELATION OF THE ADRENALS TO THE LIVER AND TO THE BRAIN IN EXHAUSTION.

Apparently adrenalin alone can cause the brain to greatly increase its work. By cross-circulation experiments, we have found that adrenalin causes increased activity of the central vaso-motor mechanism. Not only can adrenalin, as Cannon has shown, cause all the basic phenomena of exertion, emotion, infection, etc., but it also causes brain-cell lesions identical with those produced by exertion, emotion, infection, etc., including the entire cycle of hyperchromatism, chromatolysis, swelling and even disintegration of the brain cells. The injection of adrenalin causes an immediate increase in the conductivity of the brain to above the normal, followed by a later decrease to below the normal; moreover, adrenalin causes an immediate

increase in the temperature of the brain, as evidenced by thermo-couple measurements. We know that when the adrenals are excised, the brain-cells undergo a progressive cytolysis; and there is no primary stage of hyper-chromatism, but an immediate and progressive chromatolysis, edema, and final breakdown.

From these facts it would appear that the brain is profoundly, even vitally, dependent upon the adrenals; that without the adrenals, the brain rapidly loses not only its functional power, but also its power of survival. How is the influence of the adrenals upon the brain exerted? Is it the result of the direct action of adrenalin on the brain-cells? Does adrenalin owe its effect upon the brain-cells to the resultant formation of an increased amount of oxyhemoglobin in the lungs, which was demonstrated by Dr. Menten; or to its power of increasing the alkalinity of the blood? Or does adrenalin owe its remarkable effect on the brain-cells to an intermediate effect on some other organ, such as the thyroid (Aschoff, Cannon), or the liver?

That the adrenals exert also a vital influence on the liver has been demonstrated by the cytologic changes produced by the intravenous injection of excessive amounts of adrenalin—chromatolysis, edema, displacement of nuclei, loss of the power of differential staining. Similar cytologic changes in the liver cells follow double adrenalectomy. When the liver cells are thus altered, from whatever cause, the brain is unable to do its work normally, and becomes exhausted. Assuming that the *absence* or the *excess* of adrenalin causes changes in the cells of the brain and the liver characteristic of exhaustion, then does adrenalin produce these changes in the brain-cells *primarily* by acting directly on the brain, or *secondarily* by first acting on the liver? It is known that adrenalin facilitates oxidation—hence it facilitates energy transformation, and therefore, the internal respiration of the cells of each organ would be speeded up by the presence of adrenalin and diminished by its absence. The brain, being dependent on the functional integrity of the liver, and the liver being dependent in part on the adrenals, and each being dependent on oxidation, which in turn is, in part at least, dependent on the adrenals, we must conclude that the liver and the brain are not only dependent on each other, but upon the adrenals as well.

We may conclude, therefore, that the adrenals are factors in the primary cycle of exhaustion, though their role cannot be accurately defined.

THE LIVER.

Is the primary cause of exhaustion to be found in the liver? That the liver is necessary to the functional activity of the brain is proved by the following data:

(a) After excision of the liver, the power of the brain to drive the organism, to transform potential energy into kinetic energy, such as heat or muscular or mental action, is rapidly diminished and completely lost at the time of inevitable death, usually within a few hours.

(b) The brain-cells show changes in their cytologic structure which are progressive from the moment their liver is excised.

(c) After excision of the liver the temperature of the brain falls progressively until death.

(d) In every type of exhaustion from whatever cause, the cells of the liver invariably show cytologic changes, such as diminished power of differential staining, edema, and eccentric position of the nucleus.

(e) *Granting adequate circulation and respiration in a decapitated animal,* the excision of the liver causes death earlier than decapitation or adrenalectomy.

Some of the most important functions of the liver remain to be discovered, but there is one possible relation to which we may allude: The brain-cells contain almost no stored carbohydrates or neutral fats; they contain almost no factors of safety against acidosis. They have almost no stored oxygen. The brain-cells are almost wholly dependent on the blood for oxygen and for carbohydrate fuel to maintain their active and continuous metabolism; the blood is dependent on the liver for sugar for the brain. *Apparently,* for its protection against want of sugar, against intra-cellular acidosis, the brain is in part dependent on a long-distance connection with other tissues, especially the liver. The liver-cells are endowed with a great facility for autolysis; the brain-cells are but slightly subject to autolysis. We may suppose that the keen, stable brain-cells have a special chemical dependence on the remarkably unstable liver cells. For opposite reasons, then, the two organs that are most susceptible to acidosis are the brain and the liver—the brain because of its extreme activity in acid production and because of *its lack of intracellular defence against acidosis,* the liver because of its avidity for acids, possibly an adaptation for the protection of other vital organs, especially the brain. If the brain-cells contained space for the storage of reserve supplies of energy-producing material and protection against acidosis, in proportion to the space provided for this purpose in the cells of other organs, not only would the size of the brain be greatly and awkwardly increased, but its power to do work would be correspondingly diminished.

The integrity of the liver is essential to the work of the brain; and the integrity of the liver is also essential to the elimination of the acid by-products of metabolism by the kidneys and the lungs. When the liver is excised, the blood tends to become acid as the animal approaches exhaustion. The transfusion of blood, the administration of adrenalin or of morphin exert not the least check on the exhaustion and death which follow excision of the liver. On the other hand, decapitation apparently does not interfere with the function of the liver.

For its oxidizing and reducing power, the liver apparently depends, in part at least, on the adrenals; for, as we have stated above, the excessive intravenous injection of adrenalin on the one hand, and adrenalectomy on

the other, cause marked cytologic changes in the liver-cells—chromatolysis, edema, eccentric position of the nucleus.

In our electric conductivity studies we found that in exhaustion from any cause the liver and the brain were affected in opposite direction, *i. e.*, in extreme exhaustion the conductivity of the brain was decreased, and the conductivity of the liver was increased. In the earliest stages of stimulation, these changes were reversed, the period of increased conductivity of the brain apparently corresponding to the period of hyperchromatism established by our histological studies.

From these premises, we conclude that the liver is inseparably associated with the brain and the adrenals in the production of shock and exhaustion; but as the liver has no means of immediate contact with the external excitants of shock and exhaustion, it apparently in some way is influenced indirectly through the mediation of the brain.

We have now seen that *exhaustion* may be produced both *primarily* and *secondarily* by anatomical and functional defects and disabilities of the *respiratory system*, of the *circulatory system*, of the *blood,* of the *liver*, of the *adrenals.* We have seen that in exhaustion these organs and systems share in the general debility, but we have not been able to show that functional impairment of any one or of any combination of these, is the sole cause of the exhaustion of the organism in exertion, in emotion, in injury, in infection, in enforced loss of sleep, etc. If, then, the primary cause of exhaustion is not disclosed in the study of these important organs and tissues, which are either directly or indirectly driven by the master tissue, the brain and the nervous tissue, we may then ask: Is the primary cause of exhaustion to be found in the brain? Has the brain inherent elements of weakness greater than those of any other organ or tissue of the body?

The Brain and the Nervous System.
THE BRAIN AS AN ENERGY-TRANSFORMING ORGAN.

Environment, external and internal, drives the brain; and the brain either directly or indirectly drives the entire organism. Is the brain tissue itself a transformer of potential energy into kinetic energy, and does it drive the body by means of some familiar form of energy which it creates, or does the brain drive the body as a mystery organ obeying no physical laws? Is the brain capable of exhausting itself primarily by its own excessive work, or is it only secondarily exhausted?

Do the brain-cells transform much or little energy? Are they active or inactive cells? That the brain transforms potential into kinetic energy, and by means of that energy drives the body, is shown by the want of power of action when the head is cut off. That the brain is not only an active, but *the most active energy-transforming organ of the body*, is held by Mathews.

The work of the brain is greater in proportion to the weight of its tissue than is the work of any other organ of the body. Alexander and Cserna state that the brain shows a consumption of 0.360 cc. of O_2 per gram minute,

while voluntary muscle showed a consumption of only 0.004 per gram minute. According to these observers, a given weight of brain tissue transforms energy about ninety times as rapidly as an equal weight of the voluntary muscles in the quiescent state. The voluntary muscles constitute 42 per cent. of the weight of the body, the brain 2 and 3 per cent. Hence, according to the findings of Alexander and Cserna, excepting when active, the brain has a total metabolism five times greater than the metabolism of all the voluntary muscles together.

From these facts, we conclude that the brain is an organ of intense metabolism. Are the brain-cells safeguarded against the factors of exhaustion?

It would appear that the brain-cell is evolved stripped to its decks, to fight the battle of life; as if its function as an energy-transformer were so important that certain means of defence are withheld from the brain-cell and provided for it by other organs, e. g., protection against intracellular acidosis, against want of oxygen, against want of food. It would seem, therefore, that these vital functions are committed to other organs. The vast volume and distribution of blood in the liver, in the lungs, and in the kidneys provide for the rapid elimination of waste which is urgently necessary, especially for the safety of the brain. The extreme avidity of the liver cells for acid metabolites, coupled with the immense cellular surface exposed to the blood stream, we conceive to be one of the greatest safeguards to the brain against acidosis. The large storehouse of sugar in the liver serves as the fuel depot for the brain and as a protection against want of anaerobic oxygen. The blood stream carried oxygen and sugar to the brain; the buffer substances of the blood are a continuous protection to the brain against intracellular acidosis. *The brain-cells may be conceived as having their protective and nutritive cytoplasm evolved to function at a distance.*

From the elaborate provision for its protection, we may infer that the energy-transforming function of the brain has such high selective value in the biologic sense as to confer a selective value also on the structure and function of the liver and of the blood; for if the brain-cells thus stripped cannot transform energy fast enough to drive the muscles speedily enough to escape from the enemy, then the liver and the blood will perish as well as the brain. The more completely the liver and the blood and the lungs and the kidneys keep the brain-cells free from the impairing by-products of their active metabolism, the cleaner pair of heels will the pursuing enemy see. It would seem that if the bulk of the brain-cells were increased by stores of lifeless food, their power of attack and defence would be diminished.

The brain cannot work continuously, but a reversible process is necessary at regular intervals to restore it. This process in the higher centers is called sleep. The more intense the activation, the more needed is sleep. The brain is the only organ that sleeps conspicuously. Of great significance is the fact that the entire man spends one-third of his time waiting for the

brain to restore itself—to put itself again in the position of being able adaptively to transform potential into kinetic energy.

The dominating importance of the brain is further shown by the fact, as Mathews has pointed out, that natural selection in the higher animals has centered on the brain and on the brain alone. Higher animals compete through their brains. Hence, in the brain-cells, we have the highest development of a mechanism for transforming energy, for securing survival through adaptation.

IS EXHAUSTION OF THE BRAIN PRIMARY OR SECONDARY, OR BOTH?

There is evidence that the brain is both primarily and secondarily involved in exhaustion. Experimental evidence of the primary involvement of the brain in the processes leading to shock and exhaustion is found (a) in the histologic picture of immediate hyperchromatism followed by progressive chromatolyses*; (b) in immediate increased electric conductivity, followed by a progressive decrease below the normal*; (c) in immediate alteration in the temperature of the brain as evidenced by direct measurements with the thermocouple.* Common experience demonstrates that sudden bad news, intense fright, sudden severe pain, acute overwhelming infection, cause an immediate loss of muscular and mental power. Further evidence of the diminished power of the brain to do work in the presence of an adequate blood-pressure and respiration is seen during the early stages of physical exertion, of emotion, of fever, of insomnia, etc. Athletes in the early stage of the contest show no diminution of blood-pressure, but they do show diminished mental power.

In shock-producing trauma of animals under anesthesia, it was usually half an hour before the blood-pressure began to decline. What would be the physical power of an animal thus traumatized and disembowelled were he allowed to recover from anesthesia, even though his blood-pressure were normal? Captain Cowell found that the average blood-pressure of soldiers on active trench duty were above normal, but despite their high blood-pressure, these soldiers nevertheless had to be relieved for rest because of their fatigue.

In the course of fevers, the blood-pressure is usually higher than normal, but the man is prostrated. In the midst of acute grief or worry, the blood-pressure may not be reduced, but the power of the brain is reduced. A rabbit under intense excitation shows a blood-pressure higher than normal, but its brain-power is diminished. A brilliant student, a great military strategist, a highly trained executive may suffer a breakdown from mental overwork and be in a state of brain exhaustion, yet the blood-pressure may be normal. In the experimental laboratory, in the clinic of life, in the stress of war, we have reliable data from which we conclude that the brain may be exhausted primarily while the blood-pressure may be normal, or even

higher than normal. The brain is primarily exhausted in insomnia, in which doubtless acid by-products are not produced faster than the body is able to eliminate them. The brain is primarily exhausted by anesthetics, by cyanides, by acids, by lack of oxygen, by direct or reflex electric stimulation, by the excision of the adrenals, by the excision of the liver, etc. On the other hand, neither the brain-cells nor any other organ, nor the individual as a whole, is immediately exhausted by unlimited trauma *inflicted on areas cut off from connection with the brain by blocking the nerve supply.*

To a less degree, but markedly, is exhaustion from trauma or emotion controlled by large doses of morphin, or by nitrous oxid. Nitrous oxid diminishes the oxidation of the brain-cells and hence the brain is less driven by trauma. When exhaustion or shock from trauma is *prevented* by blocking the nerves, or when the nerves are intact, but the brain-cells are *prevented* by nitrous oxid from being excited to action, not only is the brain protected, but the liver, the adrenals, and other organs are equally protected; the blood-pressure does not fall, and the individual as a whole is almost completely protected against exhaustion. But despite the fact that the brain is the primary factor in both work and exhaustion, the brain is affected also by many secondary causes of exhaustion—defective circulation, insufficient lung ventilation, low blood-pressure, anemia, blood acidosis, hemorrhage, lack of oxygen, disease of the liver, disease of the adrenals, etc.

Apparently the more chemically receptive and reactive the tissue, and the more highly it is evolved to transform energy, the more readily is it exhaustible. Only cells have the power of transforming energy. The cell being the unit of work, the cell equally is the unit of exhaustion, and the brain-cell is the most readily exhausted.

We may conclude by repeating Sherrington's statement that *the brain is the master tissue of the body.* We have seen that the brain is the most active energy-transforming tissue of the body. We may conclude that when we speak of *exhaustion of a man,* we mean *exhaustion of his brain.* This is the central fact.

BIBLIOGRAPHY.

Alexander, F. G.: Biochem Ztsch., 1912, xlv, 127.
Bayliss, W. M.: Intravenous Injection in Wound Shock, London, 1918.
Bedford, E. A.: Am. J. Physiol., 1917, xliii, 235-257.
Bissell, W. W.: J. Am. M. Assn., 1916, lxvii, 1926. Surg. Gyn. Obst., 1917, xxv, 8-22.
Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, 1915.
Cannon, W. B., Fraser, L., and Hooper, A. M.: J. Am. M. Assn., 1918, lxx, 520-531, 531-535.
Cannon, W. B., and de la Paz, D.: Am. J. Physiol., 1911, xxviii, 64-70.
Cannon, W. B., and Hoskins, R. G.: Am. J. Physiol., 1911-12, xxix, 274-279.
Child, C. M.: Proc. Natl. Acad. Sc., 1915, i, 164-72.
Cowell, E. M.: J. Am. M. Assn., 1918, lxx, 607-10.
Crile, G. W.: An Experimental Research into Surgical Shock, 1897. An Experimental Research into the Surgery of the Respiratory System, 1899. An Experimental and Clinical Research into Certain Problems Relating to Surgical Operations, 1901. Blood Pressure in Surgery, 1903 Hemorrhage and Transfusion, 1909. Phylogenetic Association in Relation to Certain Medical Problems, 1910. Anemia and Resuscitation, 1914.
Crile, G. W., and Dolley, D. H.: On the Effect of Complete Anemia of the Central Nervous System in Dogs' Resuscitated After Relative Death, Jour. Exp. Med., 1908, x, 782-809. The Pathological Cytology of Surgical Shock. I. Preliminary Communication. The Alterations Occurring in the Purkinje Cells of the Dog's Cerebellum. Jour. Med. Rec., 1909, xx, 275-295.

Crile, G. W., and Lower, W. E.: Anoci-Association, 1915.

Elliott, T. R.: J. Physiol., 1905, xxxii, 401-467; *ibid.* 1912, xlv, 374-409.

Erlanger, J., Gasell, R., Gasser, H. S., and Elliott, B. L.: J. Am. M. Assn., 1917, lxix, 2089-2092.

Harrison, R. G.: J. Exper. Zool., 1910, ix, 787-846.

Henderson, Y.: Am. J. Physiol., 1908, xxi, 126-156; 1908-09, xxiii, 345-373; 1909, xxiv, 66-85; 1909-10, xxv, 310-333, 385-402; 1910, xxvi, 260-286; 1910-11, xxvii, 152-174; 1918, xlvi, 533-53. Johns Hopkins Hosp. Bull., 1910, xxi, 235-240.

Mann, F. C.: J. Am. M. Assn., 1918, lxxi, 1184-1188; 1917, lxx, 371-374.

Mathews, A. P.: Physiological Chemistry, 1916.

Menten, M. L.: Am. J. Physiol., 1917, xliv, 176-195.

Newman, R. O.: J. Physiol., 1912, xlv, 188-196.

Park, Roswell: New York M. J., 1884, xl, 177-181.

Pike, F. H., and Coombs, H. C.: J. Am. M. Assn., 1917, lxviii, 1892-1893.

Porter, W. T.: Boston M. and S. J., 1917, clxxvi, 248; clxxvi, 326-327. Proc. Inst. Med., 1918, ii, 24-29. New York M. J., cvi, 894-895.

Porter, W. T., and Storey, T. A.: Am. J. Physiol., 1907, xviii, 181-199.

Seelig, M. G., and Lyon, E. P.: Surg. Gyn. and Obst., 1910, xi, 146-152. J. Am. M. Assn., lii, 45-48.

Short, A. R.: Lancet, 1914, i, 731-737.

Wiggers, C. T.: J. Am. M. Assn., 1918, lxx, 508-511. Am. J. Physiol., 1918, xlv, 485-499; 1918, xlvi, 314-328.

THYROIDECTOMY—A BRIEF REVIEW OF 137 CASES.*

Joseph L. DeCourcy, M. D.

Cincinnati.

In October, 1919, I published in the American Journal of Surgery a résumé of fifty-five cases of thyroid enlargement, fifty of which were operated upon under local anesthesia with but one death. Of these, thirty-five were cases of well marked exophthalmic goiter. From July 1, 1919, to July 1, 1920, I have added to this list eighty-two cases of thyroid enlargement, with no deaths, making a group of one hundred and thirty (130) operated cases with but one death, or a mortality in all cases of less than 1 per cent. Of the last eighty cases, forty-five were distinctly of the systemic or exophthalmic type, while thirteen were toxic as regards metabolic determination, but were without distinct systemic symptoms. The remaining twenty-two were simple or diffuse parenchymatous hypertrophies, or hypertrophies of the adenomatous, colloid or fibrous type.

Of the first series of fifty-five cases, five were refused operation because of their advancement; of the second series of eighty-two cases only two were refused operation because of their advancement. One of these receiving hot water injections but left our care before we could determine any results; and the other died after remaining in the hospital only one week. In these two series arterial ligation was not resorted to in any case. This greater risk in the second series being entirely due to our greater confidence in the use of local anesthesia in these cases. A few inhalations of ether were resorted to in only one case during the enucleation of the lobes because of the panicky state of the patient. In the remaining one hundred and twenty-nine (129) cases all were performed entirely under local infiltration.

In sixty-eight cases of the second series, both lobes and isthmus were removed, leaving only a small portion of glandular tissue at each pole. In the remaining twelves cases the hypertropheid portion alone was removed.

In the first series of thirty exophthalmic cases operated upon, in twenty I removed only one lobe. Five of these cases returned for the subsequent removal of the other lobe. I have recently examined the fifteen cases in which only one lobe was removed and although they show marked improvement in systemic symptoms, yet they could not be considered cured. In seven cases the remaining lobe has undergone compensatory hypertrophy and the disfigurement of the neck therefore still remains. They have been benefited, however, to such an extent that they refuse further operation.

Of the eighty-three cases in which both lobes and isthmus were removed the improvement was immediate and permanent. Approximately forty-eight of these cases have been examined recently and although it is only a short time since some of them were operated upon, yet they all may be classed

*From American Journal of Surgery, Nov., 1912.

as cured, that is, their heart action has returned to normal and increases only slightly upon exertion.

Aside from these series five cases were treated indirectly, that is, attempts were made to eliminate focal infections when present, in order to ascertain whether or not they were the indirect causes of the toxic goiters. In two of these cases infected tonsils were removed, in another an infected Fallopian tube was removed. In the remaining two an exaggerated type of chronic constipation existed. One of these cases was operated upon and an adjustment of the bands and membranes about the ileocecal junction and the ascending colon was accomplished. This patient also had a retroverted uterus which was placed in its proper position. The other case was treated with agar and bran with occasional colonic irrigations.

These cases all seemed to improve to some extent, but none can be considered cured. The goiters have not diminished perceptibly, and the systemic symptoms still remain, so that thyroidectomy will be necessary.

After reviewing the foregoing series I have drawn the following conclusions and shall offer a few suggestions which I deem valuable.

Reaction following various surgical methods:

I believe that in removing both lobes and isthmus at one operation the resulting reaction is less marked and therefore the post-operative danger of the patient succumbing to a toxemia caused by a sudden release of the colloid material is less likely, than when only one lobe is removed, or one thyroid artery tied. In other words, I believe that the complete removal of both lobes and isthmus at one operation under local anesthesia is not more dangerous than the mere ligation of the superior thyroid artery, other conditions being equal, and I shall attempt to show this with charts which show the pulse curve. These were chosen because of the similarity of the cases as regards blood pressure, kidney function, heart dilatation, etc.

The tabulation following the charts reproduces the pulse rate and basal metabolic rate of the same cases.

I am not placing the foregoing cases as a criterion, but I have selected them because of their similarity and in order to show the reactions following the various methods in the same hands under similar conditions.

In other words, if it can be shown by sufficient clinical data and study that the total removal of the thyroid is just as safe a procedure as the arterial ligation, then many months of waiting and treatment will be saved the individual patient and I believe that harmful effects which continue to result to the other organs of the body even after two ligations will be avoided.

Sandford[1] has tabulated twenty-two cases in which the basal metabolic rate after two ligations has averaged plus 39. This rate although greatly reduced is undoubtedly harmful to the human organs when acting over a period of six to eight months, whereas with immediate bilateral lobectomy the basal metabolic rate drops to between plus 5 and plus 16, which is normal.

EFFECTS OF FOCAL INFECTIONS UPON THYROTOXICOSIS.

From the five preceding cases tabulated in which focal infections were found and eliminated we have come to the conclusion that toxic goiters in this respect resemble tuberculous glands, that is, although the increase of biochemical products may be caused by bacteria from focal infections, still their removal does not in itself constitute a cure, because the thyroid itself during these changes has become a focal infection, as it were, secreting its excess products which act as a poison to the body, just as is the case in tuberculous glands, and it must be removed in order to constitute a complete cure.

It has therefore been our practice to remove focal infections where found only as a preliminary to the removal of the thyroid and with no promise of cure, just as we sometimes treat patients suffering with tuberculous glands of the neck with tuberculin preliminary to their removal. This, however, is only our opinion based upon a comparatively few cases, and as clinical experiments dealing with focal infections progress and are more accurately tabulated a great deal may be accomplished along this line of endeavor. The failure to accomplish immediate results with the elimination of focal infections up to this time may be the inability to place one's finger upon the offending focus and to be able to say that this and no other is the focus which is accountable. That patients have been made to undergo innumerable operations of a destructive nature, as the removal of teeth, appendices, colon, etc., without accomplishing the desired results, has long been observed.

Dr. Frank Billings[2] has pointed out that it is our duty to build up the resistance of our patients against the organisms already in the tissues of the body even after the true focus has been removed. Even so I think that some improvement should be immediate after the principal focus has been eliminated, if it is to be expected at all.

TESTS DETERMINING THYROTOXICOSIS.

Many tests have been utilized and perfected in the past few years, some of which promise to aid us greatly not only in a more correct diagnosis of each case, but also in determining the proper treatment in the various forms of goiter. Chief among these is the "metabolic test" as made by the Benedict or Haldane apparatus, McCaskey's hyperglycemic test, etc. Of course all of these tests, if thought useful, should be used in order to ascertain the degree of toxicity of any given case, but we should not allow "the tail to wag the dog," that is, the surgeon should always refer to his clinical powers of observation and judgment, and to his operative experience, using every useful laboratory test available to aid him in his decision. The basal metabolic rate is unquestionably an improvement over the pulse rate, although its determinations in my hands correspond closely to the pulse rate.

EFFECT OF BILATERAL THYROIDECTOMY.

	Before Operation.		About 4 Weeks After Operation	
Mrs. Woods:	Pulse	B. M. R.	Pulse	B. M. R.
	118	plus 74	89	plus 20

EFFECT OF RIGHT LOBECTOMY.

	Before Operation.		About 4 Weeks After Operation	
Miss McDonald:	Pulse	B. M. R.	Pulse	B. M. R.
	120	plus 63	104	plus 43

EFFECT OF LIGATION OF RIGHT SUPERIOR THYROID ARTERY.

	Before Operation.		About 4 Weeks After Operation	
Mrs. B.:	Pulse	B. M. R.	Pulse	B. M. R.
	130	plus 76	124	plus 60

SELECTION OF HEMOSTATS TO DETERMINE NECESSITY OF LIGATION IN THYROIDECTOMY.

Many operators "tie off" all of their hemostats while others "tie off" only a very few, "taking a chance" with most of them, or even go so far as leaving many of them *in situ*.[3] By the first method we consume a great deal of unnecessary catgut into the wound, thereby inviting infection and causing a greater reaction in the tissues. By the second method we endanger the patient with secondary hemorrhage or hematomata.

For the past two years we have been using two different types of hemostats in all goiter operations.

The types to be used are optional with the individual operator. We use the small Kelly forceps and the large Kocher. Whenever we clamp fascia, or other structures, as muscles, etc., or small oozing points in fat, which we know will not bleed after the clamp is removed, we use the smaller forceps; whenever we clamp an artery or a large vein, or in clamping through the thyroid gland, or in clamping any structure which we know will require tying after the completion of the operation, we use a large Kocher forceps.

It might seem that this would involve a great deal of thought and loss of time; but we have found that we unconsciously pick up the proper hemostat and, if a nurse is passing instruments, that with only slight training she will hand the proper forceps.

In using this method we have found that we save time in knowing which hemostat requires ligature, we prevent the possibility of secondary hemorrhage, and we also prevent the possibility of hemotomata following operation. Leaving the clamps following lobe removal as suggested by Bartlett[4] becomes at once impractical because we save an enormous amount of time in knowing which clamps require ligature.

CONCLUSIONS.

(1) Removal of both lobes and isthmus has eliminated in large measure the necessity of preliminary ligation.

(2) Removal of focal infections in itself is not sufficiently effective in producing a complete cure in thyrotoxicosis.

(3) Basal metabolic rate determination and other tests have proven themselves as definite aids to diagnosis and treatment.

(4) Greater risk can be taken in operating under local than with general narcosis.

REFERENCES.

1. Sandiford, Endocrinology, Vol. IV, January-March, 1920
2. Billings, Discussion of Focal Infections by Fontaine. Journal of the A. M. A., Vol. 74, June 12, 1920.
3. Bartlett, "An Emergency Technic for Thyroidectomy." Journal of the A. M. A., Vol. 75, July 17, 1920.

SOURCES OF WASSERMANN ERROR AND THEIR CONTROL.*

By ALBERT FALLER, M. D.

Cincinnati.

That a biological test be of greatest practical utility it is necessary that it be as free from error as possible; but since all such tests are more or less subject to error, it becomes essential that all such possible sources be *known*, that provision may be made for their recognition and proper interpretation, and when such errors are *inherent* and *cannot* be remedied, it becomes necessary to adopt a *substitute* test or a modification, which is *free* from such error.

There is, perhaps, no biological test which has a greater field of useful application in medicine than the Wassermann complement fixation test for syphilis, which has become almost indispensable in every field of medical endeavor. It is to be *regretted*, however, that such a test should at times have its usefulness *nullified*, that it should at times be *misleading*, that its performance should occasionally lead us into greater and more *harmful* error than though it had not been performed. Such, however, is the status of the Wassermann test as it is commonly applied to-day; that these sources of error and their control may be sufficiently *accentuated* is the apology for this paper.

The causes of Wassermann error, *inherent* in the test itself, are:

1. Presence of but few antibodies, this resulting from (a) *heating* of serum; (b) *effect* of treatment; (c) early stage or so-called *latency* of disease.

2. Presence of natural anti-sheep amboceptor in quantities sufficient to disturb the proper ratio of Wassermann factors.

Noguchi has shown that during the first five minutes of heating about 40 per cent. of antibodies (reagines) are destroyed; during the next five minutes 20 per cent. disappear, and at the end of inactivation but 25 per cent. remain. Thus the necessity for *conserving antibodies*, especially in intensively treated and in early and latent cases, becomes apparent, and as these form a great part of the cases coming to us for diagnosis, it is *equally* apparent that a large percentage of these cases do not readily lend themselves to the unmodified Wassermann technique. These findings have led the writer to include an active control in every Wassermann, and he has *repeatedly* seen a barely perceptible inhibition result in a two plus positive reading. It can readily been seen how a negative report might have been rendered in these cases had the straight Wasserman technique alone been employed.

This is one great group of cases wherein the Wasserman causes us to give our patients *tacit* permission to develop tabes, paresis and visceral lues in later life.

The second great source of error is the presence of natural *anti-sheep amboceptor* in sufficient quantity to destroy the proper ratio of Wassermann factors.

Excess of amboceptor is disconcerting *only* when antibodies are few. It is the writer's experience that blood containing enough natural anti-sheep amboceptor and antibodies to cause a four plus reaction, shows *no* hemolysis when considerable amboceptor is added, but frequently *does* show effect in *one* plus cases; it is loss of *balance* between amboceptor in *excess,* and antibodies *deficient* in amount, that causes negative reactions where positives one should obtain; the smaller the amount of antibodies the more probable that excess of amboceptor will destroy a delicate balance; where antibodies exist in great number a comparatively *rough* approximation of reagent quantities may be tolerated, but in the presence of small amounts a most *delicate* manipulation is imperative.

Most human blood contains enough anti-sheep amboceptor to hemolyze sheep's corpuscles in *considerable* quantities. The writer has *frequently* found specimens capable of causing hemolysis in proportion of one-tenth cc. of serum to 1.4 sheep's corpuscles. Bauer has *based his modification* upon the natural hemolytic powers of human serum. The *complement* of human serum, while usually not in great amount, is, nevertheless, quite *constantly* present, and increases the effect of the amboceptor. The Wassermann technique, while demanding careful titration of amboceptor *added* to the test, takes no cognizance of the amount of this factor naturally present in the serum; *it does not seem reasonable* that a serum containing a great amount of amboceptor should have added to it the *same* amount of this ingredient demanded by a serum containing *little* or none of this body. It is *obvious* that each serum to be examined should be titrated as carefully as any other ingredient of the test; each serum should be *individualized;* it should be carefully titrated for its amboceptor and complement content; the presence of anti-complementary substances should be *sought* and a comparative estimation of antibodies should be made.

To correct the above errors, several modifications of the Wassermann test have been proposed; all possess *merit* and most possess as great possibilities for error as does the parent test.

Bauer, recognizing the fact that most sera contain enough amboceptor for all hemolytic purposes, performs *his* test *exactly* as does Wassermann, except that he adds no amboceptor. This would obviate *one* great source of error, but Bauer, like Wassermann, *inactivates,* and, therefore, destroys reagines, and border line cases may easily be overlooked by this method; then, *too,* some sera contain *insufficient amounts* of amboceptor, and in such cases this method would not be applicable.

Margarita Stern ignores *amboceptor* and utilizes the natural complement; she therefore does not *inactivate,* thereby preserving all antibodies. But complement is the most *inconstant* and *labile* feature of serum and it is

usually necessary to *add* complement from other sources; then, *too,* there is here danger of *excess of amboceptor,* as the amount in the serum is not utilized.

The writer considers the method of Bauer a very *useful* modification, but finds the method of Stern of very *limited* utility. Those methods requiring anti-human amboceptor will not be discussed here, as the writer has had but very *limited* experience with them.

Of all complement fixation tests, the writer considers the so-called Hecht-Weinberg test the most *widely* applicable and useful; this method is useful, not only as a complement fixation test, but because of the amount of knowledge it yields concerning the pecularities of each serum; it indicates *antibodies;* it shows the presence of *anti-complementary substance* and the amount of *amboceptor* and *complement* present; armed with this knowledge, the serologist is in position to properly interpret the significance of the *various* tests and to select the one best suited to the serum to be tested.

The Hecht-Weinberg test makes use of the natural anti-sheep amboceptor and natural complement, and is performed with *unheated* serum; it is therefore designed to overcome the great sources of error of the other tests mentioned; as performed by the writer, it also indicates the *amounts* of amboceptor and complement present. (Parenthetically, the writer would say he considers the amount of natural amboceptor of great prognostic import, as he hopes to show in a paper in preparation.)

The technique, as worked out by R. B. H. Gradwohl, of St. Louis, is as follows: Fourteen tubes are placed in a rack; into each is placed .1 cc. of serum to be examined; then into the first ten tubes is placed *descending* amounts of salt solution, in the first tube .9 cc. *descending* to .1 cc. Then in these ten tubes is placed ascending amount of sheep's corpuscles, beginning with .1 cc. and ending with .1 cc. This gives each of the first ten tubes equal volume; these ten tubes are for the purpose of obtaining the hemolytic index—the hemolizing power of the serum. In the next three tubes is placed graded amounts of antigen, .2 cc., .15 cc. and .1 cc. The last tube contains only *serum* and is the *control* tube; these four are then brought to equal volume with salt solution.

The rack is then placed in the water bath for one-half hour and shaken frequently. That tube which shows complete hemolysis of the *greatest* amount of sheep's corpuscles is then *noted,* and gives the hemolytic index. Blood corpuscles are then added to the last four tubes according to this index: if this is from one to four, we add .1 cc. of corpuscles; if from five to seven, .15 cc., and if eight or more we add .2 cc. The rack is again placed in the water bath and results read as in the Wassermann, when the control tube shows complete hemolysis.

It is the universal experience that a once negative Wassermann may *frequently* become positive; a proof that infection, however small in amount, still existed; it is the writer's experience (and that of R. B. H. Gradwohl,

who has had an enormous experience with this test) that when the blood becomes negative to the Hecht-Weinberg, it usually remains so. This, in connection with the fact that the Hecht-Weinberg is positive in the early primary stages of lues and in well treated and latent cases, indicates that the *smallest* amount of systemic infection causes reaction to this test.

To illustrate the absolute necessity for Wassermann modification and for obtaining the hemolytic index, the following cases may be cited:

Case of S. L. Hemolytic index 10, amboceptor content 14, Wassermann tests with heated and unheated serum are negative; the Bauer and Hecht-Weinberg tests are two plus positive. This is no doubt a negative Wassermann in a positive case of lues due to excess of amboceptor. This case one month ago, with an index of 6 gave a slightly positive Wassermann. Infection in this case occurred twenty years ago.

Case of R. L.: Has a chancre of seven days' duration; no other lesion apparent; hemolytic index is 10, amboceptor content is 14; Wassermann, heated and unheated, as well as the Bauer test, are negative; the Hecht-Weinberg is one plus positive. Here the straight Wassermann is negative because of the destruction of the few anti-bodies present and also because of the large amboceptor content; this content also interferes with the active Wassermann; the Bauer test is negative because of inactivation; the Hecht-Weinberg, utilizing a natural amboceptor, and preserving all antibodies, is slightly positive.

Case of J. C., a hospital case, was admitted because of suspected diphtheria; has a necrotic tonsil; hemolytic index is 10; amboceptor content is 15; all tests are four plus positive, excess of amboceptor and heating of serum not influencing results in the presence of excessive amounts of antibodies.

Case of W. T.: Has no index, both amboceptor and complement being entirely absent; gives a slightly positive reaction with the unheated Wassermann; negative to the regular Wassermann. Having no amboceptor or complement, this serum was not suited to the Hecht-Weinberg test; having no amboceptor and but few antibodies, it was not suited to the Bauer test; having no complement, it was not suited to the Stern test, and having but few antibodies, it could not be heated for the regular Wassermann. Any test, other than the unheated Wassermann, would have resulted in error. This is a well treated case of paresis, where the original Wassermann gave a four plus positive reading. This case is now negative to unheated Wassermann.

Such cases as these indicate that there is no one best method of testing all specimens of serum, and the writer wishes to *especially emphasize* this fact. If amboceptor is present in great amount, with enough antibodies to tolerate in activation, the Bauer test is acceptable; if amboceptor and complement are present in sufficient quantity, and no anti-complementary substances are present, then the Hecht-Weinberg, be the antibodies many or few; with low amboceptor and low complement content and few antibodies

assumed, and no anti-complementary substances, the unheated Wassermann; in all cases of anti-complementary substances, the regular Wassermann must be relied upon.

In conclusion, the writer would say that, in trying to *simplify* Wassermann and allied reactions, one is led far afield into the domain of ferment possibilities, and if we would make this field *free* from error, we must *increase,* rather than decrease, its complexities. The ideal condition for complement fixation work is first to become *thoroughly familiar* with the serum to be tested; titrate it as thoroughly as any other integer of the test; see where its error would most *likely* occur; and assign the chief significance to *that* test which *you* consider the *ideal* one for *that* serum.

PRIMITIVE SURGERY OF THE WESTERN HEMISPHERE.*

LEONARD FREEMAN, M. D.

Denver.

I have selected this subject for my address, because it seems peculiarly appropriate to bring before the Western Surgical Association something about the prehistoric surgery of the West, which, as far as I am aware, has not been done before.

Two causes of surgical and medical ailments were universally recognized among the early inhabitants of the Americas, one natural and the other supernatural. If the cause was not easily perceived, as was often the case, it was regarded as supernatural. The supernatural diseases were supposed to originate in various ways: by the casting of spells, by contact with some objectionable person or thing, or by the presence of something in the system, such as an evil spirit, a stone, a piece of wood, a worm or an insect. Manifestly, they came just as near to the recognition of bacteria as they could without knowing anything about them.

It must not be thought, however, that real causes were not given their due significance, if they made themselves sufficiently apparent, as often happened in surgical lesions at least. The ancient members of our profession were by no means always as childish as they are sometimes represented to be. It goes without saying that supernatural ailments can be treated by supernatural means only, which accounts for the existence of the so-called medicine-man, with his impressive fetishes, antics and incantations. In this connection it should be understood that the word "medicine" was not confined originally to material remedies, but had in addition a magical and supernatural significance. Hence a "medicine-man" was not only a physician in our sense of the word, but was also a sort of priest, prophet, magician and all-around dealer in the mysterious.

THE MEDICINE-MAN.

The medicine-man[1] was usually a person of more than ordinary tact, knowledge and intellect. In addition to being a surgical and medical authority, he also was consulted on many things concerning the spiritual and temporal welfare of his people. Although dealing extensively in the occult, he had a dignified and firm belief in himself and his methods, and was much in

1. Although the title is masculine, it is interesting to note that there were also "medicine-women," who held high places in the profession and no doubt deserved the confidence placed in them by their clientele. The costume and make-up of a typical medicine-man is well described by M'Clenachan: "The face is painted, usually red, with yellow trimmings about the eyes and mouth. The hair, always worn long, has a tuft of feathers braided in at the crown; and to braids of hair hanging about the shoulders are attached horsehairs, snake rattles, shells, etc.; over all is dusted red and yellow paint. The ears are pierced by numerous rings, and suspended from them hang shells, reaching to the shoulders. About the neck are strings of bright colored beads, with bird's claws, pebbles, buffalo teeth, etc. The wearing apparel consists of a shirt made of rawhide, leggins, breech clout, moccasins, and over all a blanket or buffalo robe. The shirt is daubed with paint, with some hideous image on the breast. The leggins are made to fit closely, but with a wide strip along the outside, to which is attached beads, bones, etc. The blanket or robe, in either case gaily adorned, is loosely thrown over the shoulders." Of the medicine-man's methods of treatment, Hrdlicka suc-

earnest in spite of the legerdemain and grotesque dress and actions that he employed to emphasize his doings and impress their importance on the observer. There is even reason to believe that his fantastic dances and gestures, facial contortions and weird chantings exercised a hypnotic influence on his patients, leading to relaxation and sleep, which may have facilitated the recovery of some who would have been given up to die by more civilized practitioners. In fact, when one comes to think of it, such things are merely an exaggeration of that "personal influence" which every physician is supposed to exercise in greater or less amount.

To a certain extent, the medicine-man was the protector of the perse-
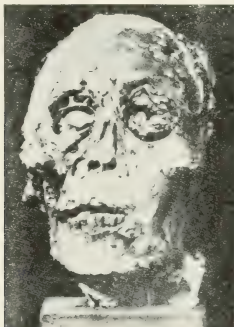
Fig. 1. Head of Peruvian mummy, showing trephine opening in left temporal region, and an apparent right facial paralysis (U. S. Ethnological Reports).

cuted, and the refuge of the fugitive. Even an enemy could find sanctuary in a medicine-lodge, where his wounds were dressed and his other needs attended to. We should indeed be proud that this same spirit has always characterized the medical profession at all times, and that it still exists among us. Looked at from this point of view, the Red Cross is a great medicine-lodge.

It was not much easier to become a "medicine-man" in those days than

emphatically says: "The treatment varies according to the supposed necessities of the case, consisting of propitiation of broken tabus, repeated prayers to the elements or deities, the deposit of prayer sticks or counter-charms in shrines, or appeal to the patient's passions, professional or totem, the use of especially effective songs, rubbing or kneading, sometimes quite violent, though employed more commonly for supposed magic effects), rubbing liquid medicines into the skin, extractions of the objective cause of the disease, blowing ashes or tobacco smoke onto the patient, passes with hands moistened with saliva, ceremonial observances or rites including painting of the body of the patient as well as that of the medicine-man and making sand paintings, noises (made with voice, rattle or drum), commands and exhortations to drive away bad spirits, assurances given the patient, various symbols, representatives, purification of the body by sweat baths, purging and emesis, strong sucking, cauterizing, sacrificing, bleeding, external applications, the administration, externally or internally, of secret magic or other medicine, and various regulations of the behavior of the patient. In the larger curative ceremonies several medicine-men acted conjointly, or, if but one present, he may have from one to several assistants."

it is now. The usual method was to spend at least a year with a preceptor, paying him well for his instruction. There was much to be learned and remembered, for these preceptors all varied in their bewildering practices, and it was customary to study under more than one. As with the modern doctor, even after graduation the life of the medicine-man was not one of pampered ease. He was compelled to respond to every call, night or day; although the Pueblos permitted an exception to the rule, if the unwilling physician could catch the messenger within a given distance and kick him. How many of us wish we had the same privilege.

If the patient died, the doctor also ran the risk of death, at the hands of the relatives; and, at the very least, a number of failures to cure led to a loss of reputation and final dismissal from the profession. There was, however, a saving clause, at least among the Pueblos, for when the medicine-man's power began to wane he could rejuvenate it by rubbing his back
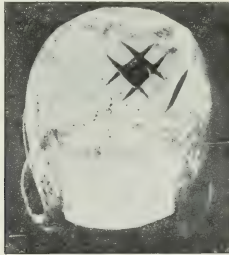
Fig. 2. Square trephine opening (U. S. Ethnological Reports).

against a certain sacred stone. The location of one of these stones is still known. The fees were of good size and paid promptly, often in advance. They consisted, not unlike those of a country doctor, of such things as blankets, horses, skins, weapons and various other personal effects. It should be emphasized, however, that to the credit of the profession much charity work was done then, just as it is now.

Curiously enough, there exists throughout the world a marked similarity in primitive medicine which suggests, perhaps, a common origin of the various races. In accordance with this, the methods of treatment were often identical among the prehistoric peoples of North, South, and Central America, including the Indians, the Pueblos, the Aztecs and the Incas. The old Spaniards were in a position to observe these things and should have been able to tell us much about them; but unfortunately those aggressive pioneers were more interested in killing than in curing, so that their descriptions are

unsatisfactory and meager. Enough has been handed down, however, to make it clear that considerable crude but efficient surgery was practiced, some of it being done in hospitals, at least in Mexico.

PRIMITIVE AMERICAN SURGERY.

Let us consider this primitive American surgery more in detail:
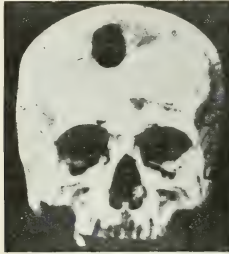
Fig. 3. Large antemortem trephine opening (U. S. Ethnological Reports).

Trephining.—As is well known, this is one of the very oldest surgical operations, and was extensively practiced by prehistoric peoples everywhere. It is probable that it was done not only for therapeutic purposes, but for other reasons as well; for instance, to let out evil spirits, to obtain amulets for decorative and other uses, or merely as a religious rite. The wearing of amulets made from sections of skulls was a common custom among the earlier inhabitants of the world. They were mostly obtained postmortem, but some were evidently removed from living captives, possibly with the idea that they were more potent as talismans against disease, or that they conferred on the wearer the physical or mental powers of the original owner.[2] But there can be no question that much trephining was also done for therapeutic purposes—for fracture, epilepsy, insanity, convulsions, headaches, etc.—as it is among various primitive races to-day.

According to archeologists, trephining was done far more frequently in Peru and Bolivia than in any other parts of the Western Hemisphere. Among 12,000 skulls from Bolivia, for example, 5 per cent. had undergone this operation, and in Peru the percentage was not much less, showing that the procedure was much more common then than now. Less is known about trephining in the United States, although occasional skulls with the charac-

2. Even in the materia medica of more modern times, powdered human skull, especially the wormian bone (known as the os epilepticus) was used as a remedy for epilepsy.

teristic openings have been found in the tumuli of the mound builders. It was more frequent, however, in Mexico and Central America.

Although many of the operations were done postmortem, others were antemortem, as is shown by the growth of bone around the edges of the openings. It may be inferred that some of the patients died during the operation, the button having been outlined but not removed. We can well imagine that a "death on the table" must have been accompanied with the same bitter regret and disappointment as it is now.

Fig. 4. Multiple antemortem trephine openings (U. S. Ethnological Reports).

We are justified in believing that these surgical interventions were frequently for therapeutic purposes, because fractures are often found in connection with them; and even when no fracture can be seen, it is not unreasonable to suppose that a puncture of the skull, such as must have been frequent from the spiked war clubs then in use, may have existed and been removed by the operation. And, in addition, the fact that the openings were sometimes at a distance from the break in the bone might well mean that the principle of decompression was recognized—perhaps learned from experience in trephining for headaches, epilepsy, insanity, etc. In fact, if we do not regard these operations as deliberate decompressions, they would seem to be purposeless.

In the Smithsonian collection is the skull of a Peruvian mummy on which the dried soft parts are still in place. A trephining has been done at the seat of a fracture in the left temporal region, the interesting point being that the face is strongly drawn to one side, apparently the result of paralysis—a most uncanny phenomenon, to say the least (Fig. 1).

Most of the trephining operations in America do not seem to have been done very skilfully. They were crude jobs with crude tools that often slipped during the laborious process, as shown by scratches on the adjacent parts of the skull.

The shape of the opening was usually square or oblong, although sometimes round or oval. The square opening (Fig. 2) was peculiar to South

America. It was made by cutting four rectangular intersecting grooves, almost but not quite through the bone, and then prying out the loosened piece of skull. The round openings (Figs. 3 and 4) were produced by gradual scraping, as shown by the characteristic of uncompleted operations.

From the nature of the grooves and the lines on their sides, it is probable that they were cut with a stone instrument, like a spear head, set in a handle and possessing a rough and rather blunt point—a kind of single-toothed, stone saw, as it were, by means of which the bone was slowly worn away by a to-and-fro motion aided by strong pressure. It is likely that the round holes were scraped out with sharp flakes of flint or obsidian, as is still done by certain more or less uncivilized tribes in various countries.

For a number of reasons, it is supposed that the patient's head was held between the knees of the operator, who laid open the scalp with a crucial incision and then sawed, scraped and pried away at the unfortunate vic-
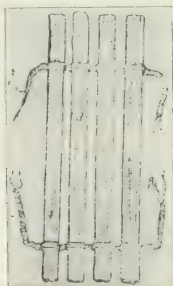
Fig. 5. Splint made of sticks held together by strips of rawhide
(Medical and Surgical Reporter, 1879, 2).

tim's calvarium, with many slips of his crude instrument, until an opening was made. The time required, as established by experiment, must have been at least an hour and often much longer.

It may have been that some sort of anesthetic was employed, such as was used by the Pueblo Indians; but if not, what a nightmare of an experience it must have been for the patient, to say nothing of the nervous strain on the surgeon; although, when one considers the matter calmly, it could not have been much worse than the torture occasionally inflicted on us by our dentists. After all, much depends on the point of view.

It should be mentioned that trephining is still practiced in the same primitive manner by native medicine-men in the mountains of Peru, although they now employ pocket knives, chisels, etc., instead of instruments of stone. The

operation is generally done for fracture, and is surrounded by great secrecy and certain mystic rites. It is said to be quite successful.

Fractures.—In the treatment of broken bones, the results were often surprisingly good. It was customary to set them, more or less skilfully, by pulling and manipulation; but permanent extension was not often, if ever, employed. Splints of various kinds were in universal use. They frequently were made of bark, the natural curves of which facilitated adjustment to the limb, especially after soaking in hot water and cutting away portions to accommodate bony prominences about the joints. Grass, scrapings from tanned hides, and other soft substances were used for padding. Occasionally the splint was filled with moist clay, which enclosed the limb somewhat
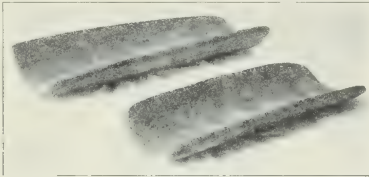
Fig. 6. Splints found in ancient cliff dwellings of southwestern Colorado (Museum of the State Historical and Natural History Society, Denver).

like a plaster cast, and must have been both comfortable and effective. A window was always left over the site of a compound fracture to permit of attention to the wound.

Other sorts of splints were made from sticks or pliable branches, such as green willows, held together by strips of bark or leather (Fig. 5). The Cliff Dwellers of the Southwest, who from their mode of life must have broken their bones often, knew how to manufacture splints that scarcely could be improved on. Specimens exhibited in the Museum of the State Historical and Natural History Society, Denver, are beautifully made from polished wood and correctly curved to fit the limbs for which they were intended, the edges being nicely rounded to prevent injury to the skin (Fig. 6). Similar splints were employed by the Aztecs.

Often the splints were removed and the limb massaged, a practice that gives good results and deserves more attention than is given to it by modern surgeons.

In the treatment of fractures, the Hopi Indians employ splinters of trees which have been struck by lightning; not, however, as splints, but merely as fetishes. For some reason or other, they believe that those who have themselves received a lightning stroke are possessed of special skill in the care of broken bones—rather a severe requirement for a specialist in fractures, one would think.

In the Field Museum, Chicago, is exhibited an excellent pair of well padded crutches from the cliff dwellings of southern Utah (Fig. 7).

Dislocation.—The reduction of many of the simpler forms of dislocation was quite generally practiced, both by extension and by manipulation, although the methods were of course empiric and without scientific foundation.

Treatment of Wounds.—The suturing of incised wounds was a common procedure; but it was considered so necessary that free suppuration should occur that thin pieces of bark were sometimes placed between the edges in order to check primary union. The sutures were obtained from animal tendons, human hair or plant fibers. The tendons were smoked hard and dry and were not absorbed, but were removed in about a week. It was cus-
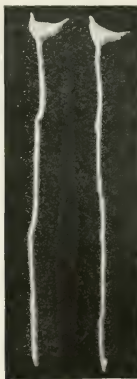
Fig. 7. Crutches found in cliff dwelling of southern Utah (Field Museum, Chicago).

tomary to provide for ample drainage, which was often facilitated by the insertion of strips of bark or other material.

The frequent washing of all sorts of wounds, perhaps several times daily, was universally practiced, and may have had much to do with the rapid, not to say astounding, recoveries that are said frequently to have occurred. The irrigations were made with simple cold water or with decoctions of certain things, such as basswood, willow, slippery elm, lichens and various herbs. In addition, the wounds were often packed with charcoal, ashes, piñon gum and other balsams, or sprinkled with these substances in the form of powder. Most of the balsams and decoctions probably had more or less of an antiseptic action, but it is questionable if this was sufficient to be of much value.

Saliva, both pure and mixed with other things, was very generally used; in fact, it was quite the proper thing for a physician to spit on a wound or into the materials used in its treatment. What consternation such a proceeding would produce in the operating room of a modern hospital! Nevertheless, we should not forget that animals always lick their injuries, and that lesions about the mouth heal even more readily than elsewhere. Another revolting custom, according to our point of view, was the sucking of pus out of wounds—a much valued method of treatment.

In Brazil, large open wounds of the extremities were sometimes handled in an extremely interesting manner. The part was wrapped in the inner bark of a tree, and suspended on a frame over a bed of glowing coals until nearly roasted. This method was painful, but is said to have been effective, primary union often resulting within a few days under the most unpromising circumstances.[3]

Although there is little evidence that actual laparotomies were ever performed, we at least know, from a description of an operation witnessed early in the seventeenth century by Bernabé Cobo, that they were sometimes "faked" for psychologic purposes. He says: "The sorcerers (medicinemen) did as if they would open him by the middle of the body with knives of crystalline stone, and they took out of his abdomen snakes, toads and other repulsive objects." However, when we remember with what dexterity the human body was opened for sacrificial purposes by the Aztecs, it should not be surprising if they sometimes performed operations on the internal organs

Punctured Wounds.—Among the Pueblos, especially, no attempt was made primarily to remove foreign bodies, such as arrow heads; but they were gradually forced out by firm kneeding and pressure applied to the surrounding parts. It was sometimes necessary to continue this painful procedure for several days, although in the end it was generally successful; but if it failed, an operation was done, through a crucial incision. Irrigations with various decoctions were frequently practiced. These were sometimes squirted deep into the openings through a quill or a hollow bone by means of the mouth or a syringe made from a bladder. Some of these primitive surgeons used sticks wrapped with cotton to swab out punctured wounds, as part of the general program of cleanliness, which, although they lacked the Dakin's solution, nevertheless reminds one of the methods of Carrel. The cleaning of punctured wounds by sucking out the pus with the mouth was an ordinary and widely spread custom, which undoubtedly possessed merit in spite of its objectionable features.

Treatment by Suction.—This was done with the mouth, either directly or through a tube of stone, wood or bone (Fig. 8). In this way pus was

3. That the North American Indians occasionally did quite good surgery is evidenced by an operation, witnessed by Cushing, on an inflamed and gangrenous foot. The trouble was supposed to be due to a mysterious maggot, and the procedure was carried out for the purpose of dislodging it. A crucial incision was made, the dead tissue excised, and the bone scraped. The wound was then repeatedly irrigated, packed with piñon gum, powdered and bandaged. The final results was satisfactory. Could a modern surgeon have done more?

removed from wounds, ulcers and abscesses, and the vascular circulation promoted, thus calling to mind the modern suction treatment advocated by Bier. Even the thought of using the mouth directly for such purposes is repulsive, but the danger to the physician was slight and the method was undoubtedly effective. After all, was it much worse than the many gruesome things done by medical students in the dissecting room? In Bolivia, at the present time, medicine-men have been seen to suck suppurating wounds and even syphilitic ulcers. Men who were thus willing to sacrifice themselves for the welfare of their patients should be respected and not ridiculed, just as we honor the young physician who heroically applies his mouth to a tracheotomy wound in a case of diphtheria.

The imaginary foreign bodies supposed to cause many diseases were also removed by sucking, being first located by the supernatural vision of the medicine-man—a sort of roentgen-ray eye, as it were. The results were made more tangible by previously placing something in the mouth, such as a stone, thorn, worm or insect, and producing it at the proper psychologic moment.

Numerous ailments were held to be due to the presence of bile in the affected part. This was sucked out directly with the mouth or through a tube, the surgeon apparently expectorating bile frequently during the process, being enabled to do so by chewing a species of yellow root in preparation for the occasion. Such procedures were of course nothing but blatant charlatanism, but they had a certain justification in the psychologic effect which they must have produced.

Cupping.—This was a common remedy. It was done by suction through a buffalo horn or a tube of wood or stone, or even by the mouth alone. Enough force could thus be exerted to cause much congestion, and an expert in the art could even raise a blister. Wet cupping was achieved by a preliminary scarification of the skin. In the Museum of the State Historical and Natural History Society, Denver, are some peculiar wooden instruments from the Colorado cliff-dwellings, labeled "use unknown," which might very well have been employed for cupping. They have a hole on one side into which a stem could be inserted to suck through, the body of the instrument being used as a handle to press it firmly against the skin (Fig. 8A).

Scarification.—This was an almost universal practice, both for local troubles and those of a more general nature. It was often done with a flake of flint, although more elaborate instruments were in use, provided with many sharp points made of fish spines, flints, etc. A method employed in Brazil was to make a number of cuts in the skin through which was inserted a stone instrument like a spear head, which was moved about in the subcutaneous tissues—a mode of treatment that could not have been popular among primitive patients.

Cauterization.—This was much used. It was accomplished with a coal of fire, a hot stone, or by burning a little ball of cotton or other inflammable substance on the cutaneous surface. Among other things, indolent wounds and ulcers were often stimulated by cauterization, and it was also employed as a counter irritant in various painful affections. A favorite method was to burn tobacco or some other material in a tube made of stone (Fig. 8B), and then blow the hot smoke through the tube on the area to be treated, decided virtues being attributed to the kind of smoke employed.

Phlebotomy.—This was extensively used in the treatment of local inflammation as well as many general diseases, being considered almost as

Fig. 8. *A*, peculiar wooden instrument with cupped end (depth not well shown) and with a hole on one side slanted upward, into which a hollow reed could be inserted; possibly used for cupping, by pressing the hollowed-out end against the skin, and sucking out the air through the reed. *B*, cliff dweller's stone pipe, also used for cupping and in the suction treatment of abscesses and suppurating wounds (Museum of State Historical and Natural History Society, Denver).

much of a cure-all as it was with our medical forefathers. The vein selected was generally in the leg or arm, but occasionally in the neck or temporal region. The instrument employed in opening the vessel was made from a sharp flake of flint or obsidian, a thorn, a fish spine, or a tooth of some sort in a handle. It was driven with a quick stroke into the vein. In Brazil, a little arrow, made for the purpose, was shot into the vein by means of a diminutive bow, thus coming as near to a "shotgun prescription" as was possible under the circumstances.

Inflammations.—These were treated commonly by poultices made from plants, leaves or barks (slippery elm, etc.), by cupping, and by counter-

irritants, such as the cautery. When an abscess resulted, incision was often resorted to, and the contents were aspirated with the mouth, directly or through a tube.

Amputation.—Although not extensively practiced, amputation was undoubtedly done at times, the bleeding being checked, perhaps, by the application of hot stones, as has been observed among the Indians. An image on an ancient vase found in Peru distinctly shows the stump of a leg due to an amputation.

Hemorrhage.—The use of the tourniquet was undoubtedly understood by some, but the more common method of checking bleeding was by the actual cautery (a heated stone) or by local pressure aided often by such coagulants as spiderwebs and the fine fibers of plants.

Hernia.—Many medicine-men knew how to hold a rupture in place quite skilfully with various forms of pads and bandages; but the most remarkable procedure was that resorted to by the Pueblos, who treated umbilical hernia
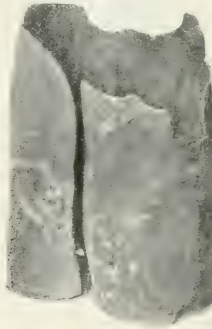
Fig. 9. Corset made of bark, with eyelets and cord for lacing it around the body; possibly used for some orthopedic purpose (Museum of State Historical and Natural History Society, Denver).

by placing on it a number of large black ants, the bites of which were supposed to have a curative effect. It would be interesting to know the origin of such an astonishing idea.

Pterygium.—Operations for pterygium were done in both North and South America, the growth being more or less skilfully removed with sharp stone knives. It was probably this operation that gave rise to the erroneous idea that cataracts were removed by these ancient ophthalmologists.

Artificial Skull Deformities.—The production of these may be considered as a sort of orthopedic surgery[4] extensively practiced by various North American Indians, as well as those of Mexico and Peru. Sometimes a board was bound against the forehead of an infant and kept there during early growth, resulting in a hideous flatness of the front of the cranium (Flathead Indians). Other tribes, such as the Vancouvers, Incas and Aztecs applied pads and tight bandages to the head in such ways as to render the skull conical, enormously elongated, or deformed in other monstrous ways. Although producing an outward semblance of idiocy, these pecularities of form did not seem in any way to influence the mentality. Flattening of the occipital region, so commonly observed in collections of prehistoric skulls, was probably more or less accidental and due to pressure of the infants' skulls against the boards on which they were habitually strapped and carried.

Anesthetics.—Although it cannot be questioned that some of our primitive peoples possessed more or less reliable methods of anesthesia, it is hardly probable that these were very generally known or employed. For instance, the Zunis and some other tribes used for the purpose of substance obtained from the jimson weed (*Datura meteloides*), containing stramonium. It was administered in sufficient amount to produce indifference to pain or even complete unconsciousness, and in this condition abscesses were opened, fractures set, dislocations reduced, and other surgical procedures accomplished. In spite of heroic dosage, no serious harm seemed to result. It is quite possible that this and similar methods were also in use among the Aztecs and Incas, who were so closely related in many ways to the Pueblos.

In this connection should not be overlooked the strong hypnotic influence undoubtedly exercised by the medicine-men, with their bizarre make-ups, weird incantations, and fantastic antics, which were well calculated to make a profound impression on their credulous patients.

4. The Museum of the State Historical and Natural History Society of Denver possesses an interesting appliance of bark made to fit the torso and provided with eyelets as though to lace it together in front (Fig. 9). It closely resembles the modern orthopedic corsets used in the treatment of lesions of the spine, and may have been used by the Cliff Dwellers for this purpose or for fracture of the ribs.

WOLFF'S LAW AND THE FUNCTIONAL PATHOGENESIS OF DEFORMITY.*

By Albert H. Freiberg, M. D.

Cincinnati.

The correspondence between the structure of bone, under normal and abnormal conditions, and the calculations of graphic statics has been made the foundation upon which a doctrine of "functional pathogenesis" has been built. It has, however, also formed the basis of numerous attacks upon this theory. The theory of the functional pathogenesis of deformity and that of the functional shape of the bones have been made corollaries to the "law of bone transformation"[1] by its author, Jul. Wolff. The "law of bone transformation" is considered by its author as deriving its greatest strength from the remarkable resemblance existing between the internal structure of the normal human femur and the graphostatic diagram of a Fairbairn crane drawn by the mathematician, Cullmann. This was given an outline similar to that of the human femur deprived of its trochanter major and viewed in coronal section, sustaining a load of 30 kilogrammes. This load is supposed to approximate that which is borne by the femur of an adult and to be applied to the crane in a manner consistent with the conditions in the human subject. The striking analogy between the courses of the bone trabeculæ in the frontal section of the femur and those of the trajectories of Cullmann's diagram was first insisted upon by von Meyer. The arrangement of the spongiosa in the sagittal section of the femur, corresponding to the "neutral plane" of the diagram, was foretold by Wolff in conformity with the demands of the graphostatic figure, and was substantiated by him later, anatomically. After the most painstaking study of the various bones of the body under normal and abnormal conditions Wolff was able to formulate his "law," which might be translated as follows:

"Every change in the form and function of the bones, or of their function alone, is followed by certain definite changes in their internal architecture, and equally definite secondary alterations in their external conformation, in accordance with mathematical laws."

Before the promulgation of Wolff's law the generally accepted theory of the development of acquired deformity was that of Volkmann[2]-Hueter,[3] namely, that consequent upon muscular weakness faulty attitude was assumed, in consequence of which one side of a joint—e. g., the external in genu valgum—was subjected to greater pressure than normal; the opposite side—the internal in genu valgum—sustained less pressure than normal. Assuming that during growth the normal development of the joint depends upon the maintenance of normal conditions of intra-articular pressure, it was explained that the increased pressure on the concave side interfered with

the normal growth of bone or even caused atrophy of that bone already formed; while on the convex (internal) side the subnormal pressure permitted an overgrowth of bone. In spite of the fact that Mikulicz[4] and Macewen[5] showed, quite long ago, that these changes in the articular surfaces and epiphyses are not constantly present in genu valgum, but that the principal deformity exists in the diaphyses of the femur and tibia, most authors continued, nevertheless, to describe the pathogenesis of this deformity in conformity with the theory of Volkmann-Hueter. We shall later see how it is better explained by reference to Wolff's law and in agreement with the anatomical conditions present.

The first corollary which Wolff's theory has associated with it is that of the "functional shape."[6] The external form and internal architecture are determined by function solely. The internal architecture and external contour always correspond exactly, the latter representing, mathematically, simply the last curve uniting the ends of the various trajectories which make up the internal structure. The compact substance is to be regarded simply as a condensation of spongiosa.

From the theory of the "functional shape" it is an easy step to that of the "functional pathogenesis" of deformity. If the internal structure and external contour correspond exactly, and if they represent an adaptation to normal function only, then an alteration in static demands made upon the bones must be followed by the proper transformations of structure, both internal and external, and as the result of these we have the "deformity in the narrower sense." The deformity is therefore to be regarded as a physiological adaptation of structure to pathological static requirements, therefore to pathological function.

The agreement of the structure of bone, both under normal and abnormal circumstances, with mathematical laws, and in particular with those of graphic statics, is insisted upon by Wolff to such an extent that it has formed the basis of attacks upon the doctrine by Bähr[7] and Ghillini,[8] as well as others. It is their object to show that Wolff's mathematical conclusions are erroneous, and that therefore it is not permissible to make deductions from them regarding the structure of the bones in their normal or pathological relations.

We may well ask ourselves, on this account, whether mathematical proof of the competency of nature's design in bone structure has been brought by Wolff in Cullmann's drawing of the Fairbairn crane and the deductions following. What is required to enable us to construct the graphostatic diagram of the femur? It must be understood, as a preliminary in answering this question, that when "mathematical proof" is spoken of mathematical accuracy is implied. It is by no means enough to say that a striking similarity exists between the diagram and the bone whose mechanics we are trying to solve. There must be absolutely no divergence between the two.

In order that the mechanics of the femur shall be submitted to mathematical proof, we must know every possible stress to which the bone is to be submitted under normal conditions, and these stresses must be expressed in figures. There must be possible of expression in figures the physical characteristics of the material used in the structure. But bones are evidently constructed of sufficient strength to withstand unusual stress without giving way. This fact is demonstrated in every-day life. How shall we calculate this "factor of safety." We may believe, with Wolff, that the femur is burdened like a crane, or with his opponents that this is not so; but the fact remains that Cullmann's diagram is computed without mention of the muscular stresses upon the bone—without reckoning with the stresses put upon the bones in other positions than the upright. The great trochanter has been omitted from consideration altogether. This is obviously not permissible in a mathematical calculation, because it is always present, because it is the means of transmitting very considerable stress to the femur, and because its internal structure is evidently continuous with that of the upper end of the femur. I am assured by experts that the proper calculation of the construction of the femur upon exact mathematical lines is a work of great magnitude, requiring not only uncommon ability, but, on account of the enormous complexity of the problem, demanding a very large expenditure of time. To my knowledge, no such exact mathematical demonstration has yet been made. In addition to this, it is by no means certain that the "factor of safety" could be calculated; this factor might well make the mathematical solution impossible. Until exact mathematical proof is brought, however, there would seem to be no warrant for saying thus definitely that the external contour of a bone represents mathematically the last curve uniting the ends of the various trajectories which make up the internal structure—for assuming that the compact substance is to be regarded simply as a consolidation of those trajectories coming from the spongiosa.

If we are unprepared, however, to acknowledge that a truly mathematical demonstration of the structure of the bones has been made, we are, on the other hand, entirely unwilling to reject the law of transformation and its corollaries on this account without further investigation. In declining to accept the analogy between Cullmann's diagram and the structure of the femur as a truly mathematical demonstration of the latter, we are, furthermore, far from saying that if such computation and graphostatic figure were made it would not coincide with the architecture of the bone. On the contrary, the structure of the femur having been shown by many years of observation to be constant, the similarity between it and the mathematical figure is so striking as to make it seem reasonably certain that the trabeculæ do represent lines of force which nature aims to resist by the laying down of the bone tissue. This is, however, far from being mathematical proof, and, as it seems to us, does not afford justification for considering some of

Fig. 116

Wolff's other conclusions as "mathematical," however true they may be otherwise shown to be.

In view of the necessarily great variation in the factors of weight-bearing and muscular stresses which must exist in mammals other than man —because of the deviation from the erect position of the trunk and because of the participation of the thoracic extremeties in the weight-bearing function, it would seem likely that much information could be obtained from the study of their bones. Able and exhaustive investigation has already been made in this direction by Zschokke,[10] Schmidt,[11] and others. It has seemed worth while to independently repeat some of this work as well as to seek further for information in the structure of other mammalian bones. The femur has been chosen as the bone for further comparison, because of its size and static importance and because it has formed the basis for most of the conclusions which have already been drawn. In examining the femora to be presently described the method reported by Wolff[9] was employed. Sections were cut by hand by means of a saw. These sections were then photographed by means of the Röntgen ray, and from the negative thus obtained the photographs were made which are herewith presented. As is the case with many radiographs, the negative is more instructive than the print made from it. In the smaller femora it was quite difficult to obtain prints the finer details of which would lend themselves to satisfactory reproduction.

In the description of the specimens which have been examined care has been taken to avoid as much as possible the repetition of details which coincide with the descriptions of Zschokke and Schmidt, above referred to. The following femora have been examined:

    I. Ruminantia.
        (a) Ox.
        (b) Llama.
        (c) Sheep.

    II. Carnivora.
        (a) South African leopard.

    III. Primates.
        (a) Baboon (papio hamadryas).
        (m) Orang (simia satyrus).
        (c) Gibbon (hylobates).
           (Humerus of gibbon also.)

For the privilege of examining into the architecture of the femora of the orang and gibbon, as well as the humerus of the latter, I wish to acknowledge my indebtedness to the administration of the Smithsonian Institution. Many of the other bones examined have been taken from the museum of the Cincinnati Society of Natural History.

REMARKS ON THE SPECIMENS EXAMINED.

I. Ruminantia. (a) *Femur of the Steer.* (Fig. 1.)

Relative length of the neck is short. Capital epiphysis extends laterally to a point corresponding practically with the axis of the shaft. It is covered with cartilage to this point, and is to this extent a bearing surface. The angle made by the neck is about 112 degrees.
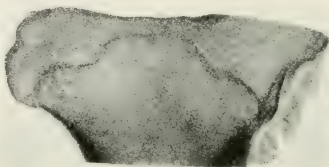
Fig. 1. Femur of young adult steer.

Arrangement of trabeculæ is perfectly constant, and corresponds with the description of Zschokke and Schmidt. The spongiosa of the young adult is composed of exceedingly fine trabeculæ. As the age increases the trabeculæ becomes coarser and less numerous, so that the internal structure is more easily read. In old animals this change has continued, so that the difference between their spongiosa and that of the young animal is most striking (see Zschokke). The three most striking systems of trabeculæ seen are:

1. *Principal pressure* trajectories (converging from the mesial part of the head to the adductor compacta).

2. Trabeculæ from adductor and abductor compacta arch toward the axis of the bones, forming a series of gothic arches whose apices are in a straight line with the lateral boundary of the capital epiphysis. Such a series of arches also exists in the trochanteric epiphysis. Orthogonal crossings can be distinguished in the system of arches.

(b) *Femur of the Llama.* (Fig. 2.)

There is practically no neck to the bone. Capital epiphysis extends to the axis of the shaft, as in the steer, but the head is set more obliquely, making an angle of 120 degrees with the shaft.

Although the animal is comparatively young (shown by imperfect union of epiphysis), the trabeculæ are comparatively coarse, their meshes large. The arrangement of gothic arches is lacking.

The marrow cavity extends comparatively high into the upper end of the bone. There are three systems of trabeculæ:
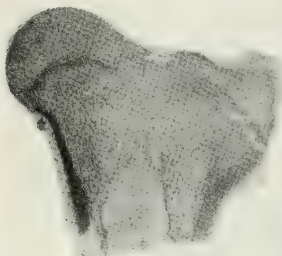
Fig. 2. Femur of Llama.

1. Principal pressure trabeculæ.
2. Two systems diverging from the base of the great trochanter.
   (a) Toward the head.
   (b) Downward to the abductor compacta.

(c) Femur of the Sheep. (Fig. 3.)

In general shape and plan of internal structure we have the steer's femur in miniature. The angle of the neck is somewhat greater (115 degrees to
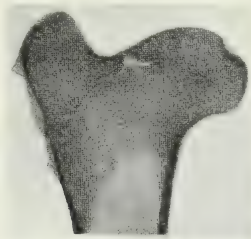
Fig. 3. Sheep.

117 degrees), otherwise the same arrangement of capital epiphysis and gothic arches, though sometimes not so easily made out. Orthogonal crossings can in part be distinguished.

II. CARNIVORA. (Fig. 4.)

The only specimen examined was the femur of a South African leopard. The femur is characterized by its proportionately long, slender, and somewhat curved neck, which makes an angle of 130 degrees with the shaft. The spongiosa is made of plates.
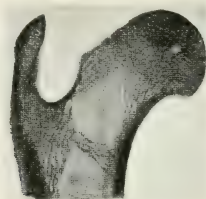
Fig. 4. Leopard.

The femoral neck presents a triangular cavity of considerable size, and which in position and boundaries would correspond with Ward's triangle of the human femur. This is separated from the marrow cavity below by a small number of arches coming from the adductor compacta and corresponding to pressure trajectories. The crossings here are orthogonal.

Shorn of the trochanter major the outline is very like that of Cullmann's diagram; the internal arrangement is, however, very different.

III. PRIMATES. (a) Femur of Arabian Baboon (Papio Hamadryas.) (Fig. 5.)

The bone is remarkably heavy for its size, and of very dense texture, so that it is difficult to saw. The neck is curved, and makes an angle of about 124 degrees.
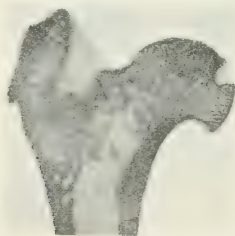
Fig. 5. Baboon.

The trabeculæ are massive, largely in the form of plates. In the head they are fairly typical as principal pressure trabeculæ, and here show orthogonal crossings, with a few tension plates. There is here, too, a cavity in the neck, separated by a few plates only from the cavity of the shaft below. The compacta of the shaft is relatively very heavy and thick, so that it is difficult to bring it into comparison with the amount of spongiosa.

Both in external conformation and internal structure the upper femoral end is strikingly like the human. The angle made by the femoral neck is 135 degrees. Both pressure and tension trajectories are found projected in a fairly typical manner, though the reticulum is much coarser than in man,

Fig. 6. Orang.

(c) Gibbon. (Fig. 7.)

the trabeculæ more plate-like. Orthogonal crossings can be made out to a limited extent. The condensation of spongiosa known as the "intermediary epiphyseal disk" (Recklinghausen), and which is constant in the adult femur, is lacking.

In general outline the upper femoral end greatly resembles that of the orang and man. The bone is remarkably light, however, its shaft very

Fig. 7. Femur of gibbon.

Fig. 8. Humerus of gibbon.

smooth and round, reminding one very forcibly of the bones of larger birds. This comparison seems all the more apt upon bisecting the bone, because of the relatively large marrow cavity, with no spongy structure whatever save at the extreme ends. The angle of the neck is 140 degrees.

The section shows a spongiosa of lamellar character, in which it is extremely difficult, if at all possible, to find an arrangement in any way similar to that of man or, indeed, of any of the femora previously described. The neck proper is practically free from spongy structure, a cavity being here found which extends to the spongiosa of the head above and to that at the base of the great trochanter below. The cellular spaces of the spongiosa are relatively very large.

In view of the contrast in functional importance between the femur and the humerus in the gibbon, great interest must attend the comparison of their internal structures. The result of it is in accord with our anticipation. The internal structure consists of a lamellar spongiosa of comparatively coarse mesh, but in its general arrangement strikingly that of the human humerus. This is true even to the existence of a place near the great tuberosity in which the spongiosa is quite rare, almost to the degree of being considered a cavity. The remains of the epiphyseal line correspond both in direction and position, and the outline is simply a miniature of the human. (Fig. 8.)

In addition, it is to be noted that the gibbon's humerus is, in comparison with its femur, heavier and denser. On holding the bones close to a bright light the shaft of the femur is seen to be quite translucent; that of the humerus is not at all so. While the humerus is a longer bone, its density is disproportionately greater than that of the femur. The volume of the two bones was determined by ascertaining their displacement of water. This was found to be 25 cc. for the humerus and 22 cc. for the femur. The weight of the humerus was 30.45 grammes against 21.67 grammes for the femur. Their ratio of weight is therefore 1.405, while their ratio of volume is 1.045. It is easily seen that the humerus is an organ of greater strength and usefulness than the femur.

In making a general comparison of the specimens in hand, it is well to remember that in graphic statics:

1. The courses of the various trajectories are dependent upon the external shape of the structures, and conversely,

2. The number of the trajectories and their size depend upon the varying factors of weight and the character of the material.

It was remarked by Zschokke—and the statement is to day equally true—that it was not possible to estimate the stresses in bone more than approximately up to that time, but that it was necessary as a matter of scientific reasoning to show, at least in some bones, that the trabeculæ truly correspond to the trajectories in direction and strength. Ten years have elapsed since this was written, but the task has not yet been performed.

Bähr, Ghillini, and the latter in co-operation with Canevazzi, have offered certain calculations in opposition, but these by no means present the solution which we seek. It would appear, therefore, that we are not yet provided with exact data to attempt a truly mathematical solution of the

mechanics of the femur. If we cling too closely to the mathematical concept of bone structure we shall find it impossible, for example, to reconcile the structures in the upper femoral ends of the gibbon and the orang. We have here a striking similarity of outline, with an equally marked incongruity of internal formation.

If, however, we depart from the strictly mathematical notion and examine into the environment and habits of the gibbon and orang we shall find an admirable adaptation of structure to these and an explanation of the great variation in internal structure. According to Flower and Lydekker,* the gibbon is by nature an arboreal creature of great lightness, accustomed to maintain itself almost entirely by the thoracic extremities. Its movements are extremely rapid, and it is able to project its body through long distances in space in swinging from bough to bough and from tree to tree. When pursued on the ground and unable to reach a tree it moves forward chiefly on its pelvic extremities, and practically in the upright position, but so awkwardly and uncertainly that it is easily overtaken by man. The humerus of the gibbon, however, belongs to the extremity of greater power and use, and is manifestly of corresponding build. In the orang, on the other hand, we find great muscular power in the posterior extremities and comparative slowness in movement. We may similarly compare the femora of the leopard and the baboon, although possibly not so aptly, the former possessing wonderful agility and ability to make enormous leaps, the latter being contrasted by the great muscular development in proportion to its size. According to Zschokke, the femora of bears able and accustomed to maintain themselves frequently in the upright position possess great resemblance to the human in their structure. So in the ruminants, also, we find the modifications of internal structure in accordance with the shortness of the femoral neck, adapted, as this is, to weight-bearing purely rather than a large range of motion.

From the above we should be justified in concluding that while external conformation and internal structure represent admirable adaptation to use, their mutual interdependence is not so exact as the strictly mathematical concept would require. If we are to modify the doctrine of the functional shape of the bones to this extent, it is probable that the doctrine of functional pathogenesis must likewise be qualified.

Valuable evidence for the theory of functional pathogenesis should be found where the function of a bone has been changed for a considerable time without any gross solution of its continuity. It is believed that such evidence can be found in the specimen of old unreduced dislocation of the hip which is next presented, and in which we have the advantage of comparison with the normal femur of the same individual.

*Mammals, Living and Extinct.

Description of Specimen of Old Unreduced Dislocation of the Hip, from the Museum of the Cincinnati Hospital (Series VII, No. 127 f).

The specimen has been in the museum for many years, and all clue to the history of the case has been lost. The board has wired upon it:

The Os Innominatum of the Side of the Luxation. This shows the acetabulum to have been unoccupied by the femoral head for a long time. The floor has become roughened by the presence of small osteophytes. The acetabular cavity appears to have become smaller by the thickening of its rim and the formation of new bone in its floor. Just behind the acetabulum there is seen a rather flat, though slightly concave, bone mass of roundish outline, with a diameter of 5 to 3.5 cm., and elevated 0.52 to 0.53 cm. above the surface of the surrounding bone. This rests upon a buttress of bone

Fig. 9. Dislocated femur.

thrown out from the ilium and ischium. It is evidently the representation of an attempt at forming a new acetabulum.

The Upper End of the Right (Dislocated) Femur. (Fig. 9.) This has been sawed through about 8 cm. below the tip of the great trochanter. It has also been bisected in coronal section.

The Upper End of the Left Femur (Normal). (Fig. 10.) This has been sawed through at 6.7 cm. below the tip of the great trochanter, the cut just striking the tip of the lesser trochanter. It has also been bisected in coronal section. Upon joining the halves of the right (luxated) femur and attempting to fit the head, in its dislocated position, into the new acetabulum, it is readily seen that its superior surface—that which formerly was the chief means of transmitting weight—was no longer a bearing surface, but that the joint bearing under the new conditions was displaced downward. It can be

seen that the position of the femur could not have been maintained by the bony socket alone, but that the soft parts must have played an important if not the chief rôle in this.

The examination of the femoral head shows at once that it may be divided, functionally, into an anterior and posterior, an upper and lower segment. The anterior segment is characterized by the smoothness of its external contour and its roundness when compared with the posterior segment, which is rough, presenting irregular elevations. The margin of the head in the posterior segment is considerably mushroomed; this is not so in the anterior. The corticalis of the posterior segment is very thin, and in one place has disappeared, so that the spongiosa is exposed. (This is not broken.) The head is no longer nearly spherical, but bullet-shaped, with a
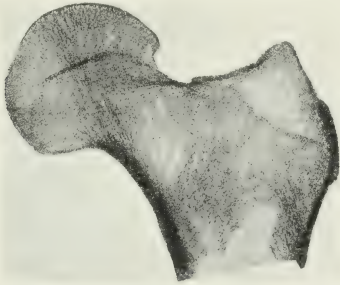
Fig. 10. Normal femur from same subject.

rounded apex in the line of the cervical axis. Crossing the anterior segment is a slight ridge which divides the anterior segment into an upper and lower portion. The upper portion is somewhat rougher and flatter than the lower, and this division will be later referred to in the description of the section.

From the anterior half of this femur a section was cut varying from 3 to 4 mm. in thickness. A similar section was taken from the left femur. Through a mishap the spongy portion in the lower portion of this section was broken. The spongy tissue should be intact through the section. The following measurements show in part the decided differences existing between the right and left femurs: Diameter from the circumference of the head to the base of trochanter major: right, 8:75 cm.; left, 10.40 cm. Height of trochanter major from tip to base: right, 4 cm.; left, 4.46 cm. Greatest thickness of adductor compacta: right, 0.58 cm.; left, 0.44 cm. Greatest thickness of abductor compacta: right, 0.57 cm.; left, 0.34 cm. Angle between the neck and shaft: right, 122 degrees; left, 127 degrees.

The following changes of external configuration may therefore be noted: (a) General diminution in the size of the bone; (b) diminution of the angle between the shaft and the neck; (c) alterations in the shape of the femoral head, as before described.

The transmutations of the internal structure are, however, more striking, and when taken in conjunction with the above-mentioned alterations of external contour, and in view of the changed conditions of stress from both weight-bearing and muscular action, make it possible for us to present a rational interpretation. These transmutations may be described as follows:

1. The cancellous tissue is of looser mesh than that of the left femur.

2. The tension trabeculæ proceeding from the abductor side are shorter in length, but also of changed (shortened) radii. The pressure trabeculæ, however, seem, if anything, more numerous and of greater strength than those of the left femur. As the result of this, Ward's triangle, which is ordinarily constituted by the convergence of two well-defined groups of trabeculæ coming from the upper part of the head and region of the great trochanter, respectively, has disappeared entirely.

3. The most conspicuous change of the internal composition is, however, to be observed in the head. We have here a considerable cavity in the spongy tissue, corresponding in position to the flattened part of the head, and which is traversed by a few bone plates. The antero-posterior depth of this cavity is 2.50 cm.; its width in the coronal section is 2 cm. The antero-posterior diameter of the head at this part is 3.40 cm. The floor of this cavity corresponds exactly with that ridge on the anterior aspect of the head which divides this into an upper and lower segment.

4. Upon examining the anterior and posterior halves of the bone, it is seen that the cancellous arrangement in the anterior segment is more compact.

Unfortunate as it is for the present inquiry that no record is left to show the exact amount of motion and strength possessed by this dislocated hip, the changes of its structure nevertheless correspond strikingly with the requirements of Wolff's law. The atrophy of the unused parts, and the condensation of those bearing increased stress, as well as the decided change of external conformation, are sufficiently manifest as to impossibly escape notice. Equally evident, however, are the encroachment upon the original size of the acetabular cavity by the formation of new bone, and the irregular surface of the unused part of the femoral head for the same reason. I take it that we have here conditions analogous to the so-called hypertrophy of the inner condyle in genu valgum, and that we are dealing with an increase in cubical dimensions as an accommodation to altered conditions of space. If this increase of cubical dimensions is to be so regarded it must be looked upon as a result of the deformity and not as one of its causes. Its functional rôle in resisting stress can, from its physical characters, be considered insignificant.

From the researches of Wolff, Zchokke, Schmidt, and others, as well as from the observations herewith presented, it is believed justifiable to conclude as follows:

1. The strictly mathematical concept of Wolff's law has not yet been justified by demonstration.

2. Save in their mathematical aspects, the statements of Wolff's law and its corollaries may be accepted as being in agreement with observations hitherto made.

3. If we accept the foregoing statements it does not follow that we must make use of the so-called "functional methods" in our therapeutic endeavors; they are to be chosen not for theoretical considerations only, but for reasons of expediency and practicability.

[NOTE.—In the discussion following the reading of this paper there was presented the right femur of an idiotic woman, thirty-five years of age, by Dr. R. Tunstall Taylor, of Baltimore. The specimen is of such interest, and is believed to be corroborative to such a degree, that, with Dr. Taylor's kind permission, the case and section of the bone are herewith briefly presented. The subject from whom it came was a paralytic, considerably deformed, having severe scoliosis and being greatly underdeveloped. The fibula of this subject was about 15 inches long and somewhat greater in thickness than a good-sized knitting needle. The pelvis was likewise deformed. The femur is extremely light in weight. Its extreme length is 38 cm.; the coronal diameter of the shaft at the middle is 1.3 cm. The head is greatly flattened from above downward, as may be seen from the section. The surface is marked by several deep grooves of antero-posterior direction. Otherwise the bone is of fairly normal shape, with the exception of the trochanter minor, which forms a quite long spur projecting anteriorly, leaving a deep groove between it and the upper part of the shaft. The radiogram of the section of the upper extremity of this femur is almost self-explanatory.
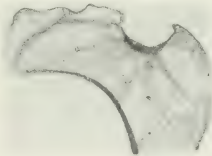
Fig. 11. Section of femoral head of a paralytic idiot, aged thirty-five years. (By permission of Dr. R. T. Taylor.)

(Fig. 11.) Vestiges of the normal internal structure are apparent. Such are the intermediary epiphyseal disk, some of the principal pressure trajectories, and some of the arches as well. The upper end of the bone is, however, merely a hollow shell, and expressive, it seems to me, not only of imper-

fect development, but of general atrophy also. As far as can be ascertained, this person was never able to maintain the upright position.]

BIBLIOGRAPHY.

1. Wolff. Gesetz, d. Transformation d. Knochen, Berlin, 1892.
2. Volkmann, v. Pitha u. Billroth's Chirurgie, ii., Abth. II, p. 693 et seq.
3. Hueter. Virchow's Archiv, xxv, p. 572 et seq.
4. Mikulicz. Arch. f. klin. Chir., xxvi, p. 5-1
5. Macewan. Lancet, September, 1884.
6. Wolff. Loc. cit., p. 80
7. Bahr. Zeitschr. f. Orth. Chir., x, p. 52, 595; Band, xii, p. 522.
8. Ghillini. Zeitschr. f. Orth. Chir., xi, p. 589; ix, p. 178.
9. Wolff. Berl. klin. Wochenschr., 1900, No. 18.
10. Zschokke. Weitere Untersuchungen ueber das Verhaeltniss d. Knochenbildung, etc., Zürich, 1892.
11. Schmidt. Zeitschr. f. Wissensch. Zoologie, lxv, p. 65 et seq.
12. Wolff. Arch. f. klin. Chir., Band liii, Heft 4
13. Wolff. Ueber d. Wechselbeziehungen zw. d. Form u. d. Function d. einzelnen Gebilde d. Organismus, Leipzig, 1901.

THE ATROPIN TEST IN THE DIAGNOSIS OF TYPHOID INFECTIONS.*

Alfred Friedlander, M. D. (Cincinnati)

and

Carey P. McCord, M. D. (Detroit)

Chiefs of Medical and of Laboratory Service, respectively,
Base Hospital

Camp Sherman, Chillicothe, Ohio

With all appreciation of the minimizing effect of typhoid-paratyphoid prophylaxis on typhoid infections in army camps, it is still reasonable to anticipate the occurrence of occasional camp cases. The larger number of such cases will probably arise from among unvaccinated civilian workmen and from the improperly vaccinated soldier. In typhoid infections appearing in persons who have received typhoid prophylaxis completely or incompletely, the disease will usually be characterized by such mildness as not to present the outstanding features of typhoid that so readily permit a diagnosis among the unvaccinated. Facing this difficulty in the recognition of typhoid existence, those medical officers responsible for the prevention of infectious diseases in army camps, and those on whom will devolve the care and treatment of suspected cases, are evaluating all recent developments purporting to be of additional diagnostic aid. At a similar period in the making of the British Army there came into use the atropin test as a means for the detection of typhoid infections. The British Medical Research Committee has sanctioned this test's reliability to the extent of issuing a monograph on the subject, prepared by Marris.[1]

In this hospital up to the present time no cases of typhoid have occurred; but in order to be conversant with the merits and technic of the atropin test against the contingency of typhoid outbreak, 228 cases of diverse diseases other than typhoid and paratyphoid have been tested in the manner described by Marris. The results form the basis of this report.

THE RATIONALE AND TECHNIC OF THE ATROPIN TEST.

According to the sponsors of this test, the normal individual or the patient ill of diseases other than typhoid infections responds to the administration of atropin with a noteworthy increase in heart rate. In typhoid patients, however, this acceleration either does not occur or occurs to a lessened degree. This difference is attributed to an antagonism of action between the alkaloid and the toxins produced by the organisms of the typhoid group. This relative lack of response to atropin is the basis of the test, the application of which is as now noted:

The patient lies horizontally and is instructed to remain completely at rest throughout this test, which is not employed until at least one hour has elapsed from the last meal. The pulse rate is counted minute by minute until it is found to be steady; ten

minutes of such counting usually suffices. Atrophin sulphate is then injected hypodermically in the dose of 1/33 grain, preferably over the triceps region to insure rapid absorption. An internal of twenty-five minutes is allowed to elapse, and the pulse rate is again counted, minute by minute, until it is clear that any rise which may follow the injection has passed off; fifteen or twenty minutes may be necessary for this purpose when the pulse rate is raised at the first count.

If, for example, a near constant pulse rate of 70 was exhibited at the preliminary counting, and a maximum of 96 was exhibited at the pulse rate subsequent to atropin injection, the inference after this acceleration of twenty-six beats per minute would, under the provisions of the test, be that the condition was not typhoid. If, however, the rate after atropin had attained only to 78 beats per minute as the maximum, the inference is tenable that the existing condition is one of the typhoid group. The test does not discriminate between typhoid and paratyphoids A and B. In Marris' report, the line of demarcation for the interpretation as existing typhoid or nontyphoid is placed at fifteen; that is, if the acceleration following atropin is less than fifteen beats per minute, typhoid is indicated; if the increase is fifteen or more per minutes, typhoid is not indicated. A "positive" atropin reaction is one giving rise to little or no increased heart rate after atropin administration (fourteen or less per minute). A "negative" reaction is one giving rise to an increase of fifteen or greater.

If the patient is admitted during the first fortnight of his illness, the test is applied as soon as possible after admission and is charted with the temperature. When a positive reaction (little or no response to atropin) is obtained, the diagnosis of infection with a member of the enteric group of organisms may be made. In the case of a negative reaction, the test should be repeated after two or three days, and if again negative, it is again repeated. Three negative reactions falling within the first fortnight of the illness exclude the presence of typhoid with a considerable degree of certainty; there are rare exceptions, and in these a continuation of the test is usually suggested by the symptoms and remaining clinical signs.
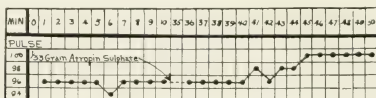
Chart 1. Typical positive atropin test in measles patient presenting clinical manifestation similar to those of the patient whose reaction is shown in Chart 2. The broken line after the administration of the atropin represents an interval of twenty-five minutes.

In the normal individual to whom has been administered 1/30 or 1/33 grain of atropin, some or all of the following manifestations may be expected to occur: A slight and transient decrease of the pulse rate (two or four beats per minute) occurs early with a return to normal. This is followed by a rapid increase in heart rate of from twenty to thirty-five beats. The height of this acceleration is reached in about one-half hour, slowly returning to normal in one or two hours. The classical characteristics of atropin action, lessened secretions and dilated pupils, seldom are observable during the

testing period, but at times may be noted within an hour or more subsequent to the testing.

Marris' report records 111 cases of typhoid infections in which a diagnosis was definitely established through the isolation of the organism from blood cultures. The atropin test was accurate in 98 per cent. In these cases the pulse acceleration averaged only 6.6 beats per minute. In another group of patients observed by the same writer, of 247 diagnosed by the less definite agglutination method as having typhoid, 222 reacted accurately to the test. Agglutination as a diagnosis procedure has become of less value because of frequent agglutination concomitant to typhoid prophylaxis.
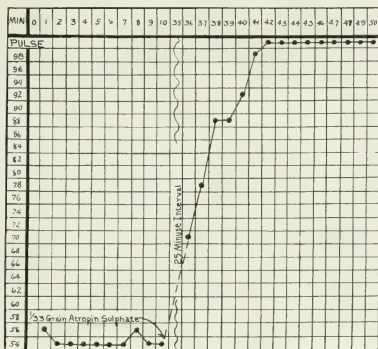
Chart 2. Typical negative atropin test in measles patient presenting clinical manifestation similar to those of the patient in Chart 1.

At the Royal Victoria Hospital in Montreal, Mason[2] made use of the atropin test as a diagnostic aid during an epidemic of typhoid infections. The technic employed was essentially that described by Marris. In all, 265 tests were made in sixty-three cases of typhoid or paratyphoid. Fifty-six of the number were cases of typhoid fever established by positive blood cultures or by Widal reactions in dilution higher than one in forty. Five of the cases were paratyphoid B, diagnosed bacteriologically, while the remaining two cases were clinically typhoid but the diagnosis was unconfirmed by any bacteriologic or serologic findings. Of the total number (sixty-three patients), fifty-seven were males and six were females; no sex variations were observed. Eleven of the sixty-three failed to give a positive reaction to the atropin test. This departure from the anticipated posi-

tive reaction is attributed by Mason to be due in part to the fact that in certain cases only one test was carried out, in part to the restlessness of some of the patients under test conditions. The reaction became positive about the tenth day and disappeared about the thirty-first day of the infection. As a check for these known typhoid and paratyphoid cases, the test was applied to forty-six patients suffering from various clinical conditions other than the typhoids. Forty-three yielded the anticipated negative reaction, averaging in cardiac acceleration 21.5 beats per minute. Three gave positive
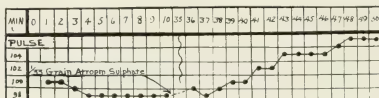
Chart 3. Typical positive atropin reaction in pneumonia patient whose clinical condition was the same as that of the patient in Chart 4. Broken line, interval of twenty-five minutes

reactions without any probability of enteric infection. Mason concludes that in the diagnosis of fevers of the typhoid group, the atropin test is of distinct value and in many cases affords diagnostic data prior to a positive Widal reaction.

TECHNICAL DATA FROM THE PRESENT INVESTIGATION.

Early in our series of tests it was obvious that our results would be at variance to the foregoing, for which reason it was deemed desirable that our technic should conform in as many respects as possible to the previous work. This necessitated the discarding from our series the results from fifty-eight cases in which technical innovations had been introduced. In the remaining 170 cases, 198 tests have been carried out with rigid adherence to the Marris technic. The patients on whom these tests have been made were all men, predominantly of the third decade. All had received typhoid-paratyphoid prophylaxis. These men were patients suffering from the diverse conditions given in the accompanying table. In one group of 170 cases, 108 (63.6 per cent.) were sensitive to atropin (atropin negative test), while sixty-two (36.4 per cent.) were nonsensitive to atropin, giving the reaction described as typical for typhoid infections. Neither the positive nor the negative atropin tests were sharply associated with any particular conditions. It may be observed in the table that in the various listed processes, the positive and the negative are almost uniformly distributed in the ratios noted above. Charts 1 and 2 are records of the occurrence of distinct positive and negative atropin tests, respectively, obtained in two measles cases similar in clinical characteristics. Charts 3 and 4 likewise were obtained, respectively, in two cases of lobar pneumonia of approximately the same degree of severity and at about the same stage of the process.
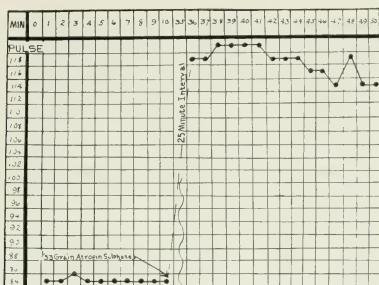
Chart 4. Typical negative atropin reaction in pneumonia patient whose clinical condition was the same as that of the patient in Chart 3.

On two successive days the atropin test was made on twenty-seven patients thus distributed: influenza, 11; pleurisy, 3; pneumonia (lobar), 2; pneumonia (bronchial), 1; bronchitis, 4; tonsillitis, 5; ethmoiditis, 1.

RESULTS OF TESTS.

Diagnosis	Total Number of Cases	Number Sensitive to Atropin, Negative	Number Nonsensitive to Atropin, Positive
Measles	39	17	22
Scarlet fever	18	6	12
Influenza	23	19	4
Tonsillitis	8	5	3
Laryngitis	1	1	0
Pharyngitis	2	2	0
Bronchitis	6	5	1
Pneumonia	22	13	9
Pleurisy	3	2	1
Bronchopneumonia	11	9	2
Mumps	1	1	0
Mumps-measles	2	2	0
Meningitis carrier	9	6	3
Diphtheria carrier	5	4	1
Diphtheria	1	1	0
Ethmoiditis	2	2	0
Neuritis	1	1	0
Adenitis	3	2	1
Gastric ulcer	1	0	1
Intestinal stasis	1	0	1
Hyperchlorhydria	2	1	1
Arthritis, chronic	2	2	0
Tuberculosis, pulmonary	1	1	0
Jaundice, catarrhal	2	2	0
Tapeworm	1	1	0
Heart block	1	1	0
Hyperthryroidism	1	1	0
Secondary anemia	1	1	0
Total	170	108	62

It was observed that of the total number, fifteen patients were atropin sensitive on both days, four were atropin nonsensitive on both days, and eight were within the limits of atropin positive on one day and atropin negative the other day. The last named group of eight may not be cited as evidence of shifting from an atropin sensitive to an atropin non-sensitive state, for the pulse rate changes were such as to fall in one day's test just above or just below the arbitrarily chosen line of demarcation, and on the following day to fall on the opposite side of the line without there having occurred an actual pulse rate variation of more than six or eight beats. Apart from these borderline cases, the results obtained on the two successive days were closely alike, as shown in the plotted results in one case (Chart 5).

In none of the sixty-two cases giving rise to results that under the provisions of the test would be interpreted as typhoid infections were there evidenced any clinical or laboratory findings that might remotely be attributed to typhoid or paratyphoid fever.
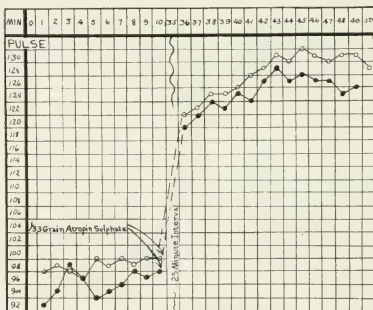
Chart 5. Conformity of results of two negative atropin reactions made on successive days in a patient convalescing from lobar pneumonia.

COMMENT.

The conception of a specificity of antagonism of action between atropin and typhotoxins is in no way borne out by the results of our investigation. The occurrence of 36.4 per cent. positive atropin reactions in a series of 170 nontyphoid cases removes from this test all but the most casual significance as a diagnostic procedure. The factors that determine the degree of response of the heart to atropin action are fundamentally the outgrowth of variations in the equilibration of the vegetative nervous system. This lack of sensitiveness to atropin is not peculiar to typhoid infections, but is detect-

able in many diseases and, in fact, may frequently be elicited in normal individuals as a mark of vegetative nervous system instability.

Not only in other conditions than typhoid is this insensitiveness to atropin encountered; but also in typhoid infections marked cardiac acceleration may be observed, according to Matsua and Murakami,[3] who say: "In our forty-six cases of typhoid fever (including seven cases of paratyphoid B), atropin was quite active, accelerating the rate of pulse, especially in cases of brady-cardia. As all our cases were serologically and bacteriologically controlled, the diagnosis was undoubtedly correct." It is noteworthy that such typhoid patients as exhibited a bradycardia exhibited cardiac acceleration after atropin, while the patients presenting a relative tachycardia were for the most part unaffected by atropin. In the series cited by Matsuo and Mura-kami, all the fatalities occurred among the number giving positive atropin reactions. This observation is in keeping with the well established fact that a tachycardia in typhoid bespeaks a pessimistic prognosis. The atropin re-action for this reason may attain to definite prognostic value.

SUMMARY.

A series of 170 nontyphoid patients has been tested with the atropin reaction in the manner described as reliable for establishing the presence or absence of typhoid or paratyphoid infections. Thirty-six per cent. of the number examined yielded results characteristic of typhoid. Those cases giving reactions typical of typhoid without any evidence of typhoid existence were distributed over thirteen diseases. It is concluded from so high a percentage of discrepancies that the atropin reaction is without especial value in the detection of typhoid infection.

3. Matsuo, Iwao, and Murakami, Junichi: Pharmacodynamic Examination of the Vegetative Nervous System in Typhoid Fever, Arch. Int. Med., March, 1918, p. 399.

NOTE ON THE INFLUENCE OF FOOD UPON THE INTESTINAL FLORA OF INFANTS.*

By Alfred Friedlander, M.D.,

AND

J. Victor Greenebaum, M.D.,

Cincinnati.

(From the Laboratory of the Cincinnati Hospital; Director, Dr. P. G. Woolley.)

As a preliminary to the studies about to be reported, routine stool examinations were made on fifteen marantic infants, all under one year of age, in the children's ward of the Cincinnati Hospital. The following schedule was observed: The stool in each case was collected on sterile gauze, marked and placed in an ice pail till examined, the time varying from thirty minutes to twelve hours.

Every stool was examined macroscopically (size, shape, color, consistency, abnormalities, such as curds, mucus and blood). Microscopically, fats, neutral fats, fatty acids, soaps, starch, crystals, abnormal constituents such as cells.[1]

A Gram smear was then made and inoculation made into the various media to be mentioned. This technique was followed in all cases except that in the study of the two special cases the stool was collected by means of a sterile anal tube after the method of Kendall.[2]

Routine examination for the bacillus aerogenes capsulatus (B. Welchii), according to the methods of Herter[3] and Kendall,[4] showed conclusively that the gas bacillus was not a common or a constant factor in the cases studied. Forty-six tests were made in the twelve children, five cases showing a positive reaction for a total of eleven positive finds. The two cases subsequently selected for special study had seven of these eleven positive reactions. Tests for dysentery, typhoid and paratyphoid were negative in all cases.

The two special cases showed practically the same clinical picture, and, though of different ages, were taking approximately the same kind and amount of food. Their stools were similar, macroscopically and microscopically. They both presented typical marantic pictures. In both cases various food modifications, for the most part containing high percentages of maltose, cane sugar or lactose, had been tried. Neither case had done well on these mixtures. It appeared to us of interest to study the intestinal flora in these two cases in detail, attempting to ascertain whether definite change in the bacterial picture could be brought about by change of food.

This method of studying the biology of the intestinal flora was similar to that adopted by Kendall[5] in his work upon monkeys, from which he determined that putrefactive flora developed on a proteid diet, acidophilic on a carbohydrate diet. Accordingly, these two children, after a complete series of examinations of the intestinal flora had been made, were given Finkel-

stein's albuminized milk.[6] The formula of this food is approximately fat, 2 per cent.; sugar, 1.5 per cent.; proteid, 3 per cent.

Each child was given seven ounces every three hours—six feedings in twenty-four hours. The forty-two ounces for each child daily gave a caloric value of 498, and supplied 6.4 grams nitrogen. We selected this food for the following reasons:

(1) The children had both done poorly on food with higher sugar content.

(2) For the well-known therapeutic effect of lactic acid bacilli in cases showing presence of gas bacillus (which both these children had done).

(3) To obtain the high proteid in proportion to sugar content.

(4) To determine the effects clinically, and from the standpoint of intestinal flora biologically, upon cases for whom *a priori* such food might be considered indicated.

After the children had been upon this albuminized milk for three weeks, complete series of bacteriologic tests were made at intervals of a week, using stools collected by the anal tube for this purpose. Daily examinations of stools collected in the ordinary manner (sterile gauze, ice pail) were also made. The day after the second anal tube specimen was obtained (the children had been on the Finkelstein milk for four weeks) the food was again changed. The children were now given a mixture containing approximately fat, 2 per cent.; sugar, 7 per cent.; proteid, 3 per cent. made by modification of certified milk.* Each child was given seven ounces of this mixtures every three hours—six feedings in twenty-four hours. This food has a caloric value of 791, and a nitrogen content of 6.4 grams.

This food was selected because:

(1) The children, though in better general condition while on the Finkelstein diet, did not show a sufficient increase of weight. An increase of the caloric value of the food was thus indicated. We chose to increase the sugar, using lactose, because from our experience in the Cincinnati Hospital and the Boston Floating Hospital we had not found the lactose as injurious as the Finkelstein school would make it out to be. Besides the children had previously had other sugars without good effect.

(2) To replace the salts which the Finkelstein food reduces.

(3) Because examination now showed absence of gas bacillus, so that excessive amounts of lactic acid bacilli were not needed.

The same observations and bacteriologic tests upon specimens obtained with the anal tube were made, after the children had been taking the food for three weeks and were repeated one week later. As before, daily examinations of stools obtained in the ordinary way were carried out.

The routine bacteriologic tests carried out in both cases consisted of inoculations of fermentation tubes of sterile milk, broths with 1 per cent. each of saccharose, dextrose and lactose; 2 per cent. dextrose, with 0.6 per

---

* 11 ounces 10 per cent. milk, 63 ounces fat free milk, 12 ounces boiled water, 25 ounces milk sugar quantity for both cases.

cent., or $^N/_{10}$, acetic acid, and 1.2 per cent., or $^N/_5$, acid, aerobic gelatin stabs, milk and litmus milk test tubes, anaerobic gelatin test tubes (Wright's method), and both gas bacillus tests were made daily. Gram smears of the fermentation tube sediments were made at the end of five days. The detailed bacteriologic findings, together with details as to chemical and microscopic examinations of the stools, are attached to this report.

The condensed report of the two cases follows:

CASE I.

Hazel Reed. Aged eight months in November, 1911. Admitted to hospital August, 1911. Diagnosis at that time, gastroenteritis. Typical atrophic picture.

PERIOD I. Entrance to November 18, 1911.

Foods Used.—Various modifications of milk and barley water, formulæ containing high percentages of maltose, cane sugar and lactose. General condition during this period changed but little. On entrance weight was seven and one-half pounds. There were occasional slight gains, but the general trend was downward until at the end of the period the weight was six and one-half pounds. Temperature practically normal throughout the period.

The stools averaged one to two per day, soft to pasty green, with occasional curds and mucus. They showed fatty acid crystals in abundance. Gram fecal smears: Gram negative always with one exception. Two presumptive reactions for gas bacillus out of five tests.

PERIOD II. November 18, 1911, to December 20, 1911.

Food Given.—Albuminized milk (Finkelstein). Slight but steady gain in weight to eight pounds, a gain of 1.3 pounds in four weeks. The temperature remained normal. Urine showed no indican. The stools averaged one per day, constipated, grayish-yellow, no curds. Microscopically, some fatty acids and crystals. Reaction, alkaline. Gram fecal smear: Gram negative predominate, Gram positive once.

Bacteriology.—Stools collected in ordinary way. Two presumptive gas bacillus tests two and three days after the food was begun, negative after that. Considerable activity in milk. (Stormy fermentation.) Gelatin: Considerable liquefaction and gas. Litmus sugar and broth test tubes—acid and occasional gas. Anal tube stools: Considerable activity in all media. See summary in chart.

PERIOD III. December 20, 1911, to January 15, 1912.

Food.—Certified milk modification. Fat, 2 per cent.; sugar, 7 per cent.; proteid, 3 per cent. General condition strikingly improved. Rapid gain of weight, one-half pound in first four days. Total gain of 2.4 pounds in twenty-six days. Temperature practically normal throughout the period except for one period of thirty-six hours. The lower incisor teeth appeared at this time. Stools, one to two daily, soft to pasty yellow with occasional curds (proteid by formalin test). Fatty acids and crystals.

Gram fecal smears: Negative predominate.

Bacteriology.—No presumptive gas bacillus tests. Somewhat less activity in milk and gelatin, liquefaction present but decreasing.

Anal tube stools: Somewhat less activity in media, but same types of reactions were present. See summary in chart.

We had thus definite and striking changes in the general condition and weight of the child and in the gross character of the stools in both the second and third feeding periods. (Albuminized milk and modified certified milk.) The improvement was much more marked in the third than in the second period.

There was absence of any striking change in the Gram smears and bacteriologic reactions of the intestinal flora, merely a gradual decrease in general activity in the third period.

There was absence of gas bacillus reaction after the third day of Finkelstein diet. The child continued to gain in weight after the conclusion of the third experimental period and was discharged in excellent condition.

CASE II.

Lizzie Clifford, aged about one year in November, 1911. Admitted September, 1911. Diagnosis, gastroenteritis. Typical atrophic picture.

Period I. August, 1911, to November 18, 1911.

Food.—Milk and barley water formulæ containing high percentages of maltose, cane sugar and lactose. Formula, fat, 3 per cent.; sugar, 3.5 per cent.; proteid, 2.8 per cent.

The general condition showed no particular improvement. The weight, which on entrance was 10.6 pounds, showed slight gains and losses, but in general remained about the same. As a rule, the temperature was normal. Stools one to two daily—yellowish-green with frequent curds and mucus. Constipation at times; castor oil given frequently.

Microscopically, the stools showed a moderate amount of fatty acid crystals and soap. Gram fecal smears were generally negative; positive twice. One presumptive gas bacillus reaction out of three tests.

Period II. November 18, 1911, to December 20, 1911.

Food.—Albuminized milk, given in same manner as in Case I. The general condition was distinctly better. There was an increase of weight of one pound in four weeks. Temperature normal. Urine showed no indican. Stools: One, rarely two per day, pasty yellow, no curds or mucus.

Microscopically, a few fatty acid crystals, some soap. The Gram fecal smears were predominantly negative, positive three times out of ten examinations.

Bacteriology.—Gas bacillus reaction on third and fourth days after the Finkelstein food was begun, but negative thereafter; stools obtained in ordinary way showed acid and some gas on litmus sugar and broth test tubes. On milk and gelatin there was no particularly active reaction. The anal tube specimens showed marked activity on all media. (Summary on chart.)

CHART I.—HAZEL REED.

SUMMARY OF REACTIONS (AT HEIGHT) WITH GRAM SMEARS OF SEDIMENTS.

Date and Post.	Gram Fresh Sugar	Milk Test	Litmus Milk	Aesculin Gelatin	Anaerobic Gelatin	Anaerobic deep agar	Lactose	Dextrose	Saccharose	2% Dextrose Ferm. Tube with Aortic Acid	2% Dextrose Ferm. Tube with Aortic Acid	Milk Ferm	Gas Bacillus Test Test Tube	Ferm Tube
Dec. 11, 1911. Finkelstein.		Coag. and gas in 1 day. Digestion and alkaline on days.	Coag. and acid in 1 day. Alkaline, digestion, on days.	Liquefaction, complete, 14 days.	Liquefaction, nearly complete, 14 days.	Clostres. 4 cm. 4 days. Gram +	Cloudy and gas. 0.75 cm. 1 day. Gram +	Cloudy and gas. 2.2 cm. 4 days. Gram +	Cloudy and gas. 2.2 cm. 4 days. Gram +	Clostres. 3 days. Gram +	No change Gram	Coag. in 1 day. Gas 0.75 cm. 6 days. Gram +		Coag. and gas
Dec. 18, 1911. Finkelstein.		Coag. and gas in 1 day. Acid, on days.	Coag. and acid in 1 day. Alkaline, days.	Slight liquefaction, 14 days. 13.5 cm. wide 60 days.	No liquefaction, on days. carbonacous growth.	Cloudy and gas. 0.6 cm. 4 days. Gram	Cloudy and gas. 2.9 cm. 4 days. Gram	Cloudy and gas. 4 cm. 4 days. Gram	Cloudy and gas. 0.6 cm. 3 days. Gram	No change Gram +	No change Gram	Coag. and gas 1 day. Gram +		
Jan. 8, 1912. Modified Milk Fat 2⅝ sug.		Coagulation, 1 day.	Coag. and acid in 1 day. completely acid, 15 days.	Liquefaction, 1.2 cm. deep 11 cm. wide 24 days.	Liquefaction, 1.5 cm. deep. gas tubing, 24 days.	Cloudy and gas. 0.9 cm. 1 day. Gram	Cloudy and gas. 0.9 cm. 1 day. Gram	Cloudy and gas. 4.9 cm. 1 day. Gram	Clostres. 1 day. Gram +	No redness 1 gas bubble in 1 day Gram +	Coag. and gas in 1 day Gram +		
Jan. 15, 1912. Modified Milk Fat 2⅝ sug.		Coagulation, 1 day.	Coag. and acid in 1 day. completely acid, 15 days.	Liquefaction, 2 cm. deep 2.75 cm. wide 17 days.	Liquefaction, 1.2 cm. deep. gas tubing, 17 days.	Cloudy and gas, 2.4 cm. 4 days. Gram	Cloudy and gas, 1.6 cm. 4 days. Gram	Cloudy and gas, 0.6 cm. 4 days. Gram	No change Gram	No change Gram +	Coag. and gas in 1 day. 2 cm. in 4 days Gram +		

CHART II.—LIZZIE CLIFFORD.

Date and Post.	Gram Fresh Sugar	Milk Test	Litmus Milk	Aesculin Gelatin	Anaerobic Gelatin	Anaerobic deep agar	Lactose	Dextrose	Saccharose	2% Dextrose Ferm. Tube with Aortic Acid	2% Dextrose Ferm. Tube with Aortic Acid	Milk Ferm	Gas Bacillus Test Test Tube	Ferm Tube
Dec. 11, 1911. Finkelstein.		Coag. 1 day. Digestion and Acid, 60 days.	Coag. and acid in 1 day. Acid, 60 days.	Liquefaction, 1.5 cm. in 14 days.	Liq. complete. 2.7 cm. 2 cm. further in silk 14 days. complete. 60 days.	Cloudy and gas. 2.5 cm. 4 days. Gram	Cloudy and gas. 2.5 cm. 4 days. Gram +	Cloudy and gas. 3 cm. 4 days. Gram	Cloudy and gas. 1 cm. 4 days. Gram	Cloudiness 3 days. Gram +	No change Gram	Coag. in 1 day Gas 2.5 cm. 6 days. Gram +		
Dec. 18, 1911. Finkelstein.		Coag. and gas in 1 day. Acid, 60 days.	Coag. and acid in 1 day. Digestion and alkaline, 60 days.	Slight liquefaction, 14 days. 2.5 cm. deep 1.4 cm. wide 60 days.	Slight liquefaction, 1.1 cm. 1.4 cm. wide 60 days.	Cloudy and gas. 2.7 cm. 4 days. Gram	Cloudy and gas. 3.0 cm. 4 days. Gram	Cloudy and gas. 0.8 cm. 4 days. Gram	Cloudiness 1 day. Gram +	No change Gram	Coag. and gas in 1 day Gram +		
Jan. 8, 1912. Modified Milk Fat 2⅝ sug.	+	Coagulation, 1 day.	Coag. and acid in 1 day completely acid, 25 days.	Liquefaction, 1 cm. 1.5 cm. wide in 14 days. 24 days.	Liquefaction. 1 cm. 1.5 cm. further in 14 days. 24 days.	Cloudy and gas. 1.5 cm. 4 days. Gram	Cloudy and gas. 2.7 cm. 4 days. Gram	Cloudy and gas. 0.8 cm. 4 days. Gram +	Cloudiness 1 day Gram +	Cloudiness 1 day Gram	Coag. 1 day. Gas, 5 cm. 2 days. Gram +		
Jan. 15, 1912. Modified Milk Fat 2⅝ sug.		Coagulation, 1 day.	Coag. and acid in 1 day completely acid, 6 days.	Liquefaction, 1.2 cm. 1 cm. further in track 17 days.	Liq. complete. 1.7 cm. 2.1 cm. further in silk 1 gas bubble 17 days.	Cloudy and gas. 1.8 cm. 4 days. Gram	Cloudy and gas. 2.1 cm. 4 days. Gram	Cloudy and gas. 0.3 cm. 4 days. Gram	Cloudiness 2 days Gram +	Cloudiness 2 days Gram +	Coag. 1 day Gas 1.75 cm. 3 days. Gram +		

PERIOD III. December 20, 1911, to January 15, 1912.

Food.—Modified certified milk, fat, 2 per cent.; sugar, 7 per cent.; proteid, 3 per cent. General condition strikingly improved. Child gained three pounds in twenty-six days. Temperature normal, practically during whole period. Stools, one to two daily. Pasty, yellow, soft, with occasional curds. Reaction, alkaline.

Microscopically, abundant fatty acid crystals and soap. Gram fecal smears: Gram negative with increased numbers of Gram positive organisms; Gram positive three times.

Bacteriology.—No gas bacillus reactions. Very little reaction in the milk test tubes, very moderate reaction in gelatin. Anal tubes specimens showed activity on all media, but in general less than that seen in Period II. (Summary on chart.)

The child was discharged in excellent condition. We had in this case distinct improvement in the general condition, weight and gross character of the stools in both the second and third periods, though the changes were much more marked in the third period.

There were no striking changes in the bacteriologic reactions, though there was some decrease in activity in the third period. The Gram fecal smears, however, took on a decided positive appearance in the third period. There were no gas bacilli reactions after the third day on Finkelstein's diet.

SPECIAL NOTES RELATING TO BACTERIOLOGIC FINDS NOT CHARTED ABOVE.

Milk Fermentation Tubes.—Same type of reaction with both foods.

Gram Smears.—Gram +. Occasional branched forms (probably bacillus bifidus) on both foods. Predominace of yeasts on Finkelstein's food.

Milk Test Tube.—Distinctly greater activity (coagulation gas and digestion) in Period II. (On Finkelstein's food.)

Aerobic Gelatin.—Marked activity (complete liquefaction) in first test, but second test in both cases on Finkelstein's diet showing slighter reaction than in either of tests on 2-7-3 food.

Anaerobic Gelatin.—Same as in aerobic gelatin except in general less activity. No liquefaction present on second test on Finkelstein's food.

FERMENTATION TUBES.

Lactose.—All tubes showed cloudiness and gas. Average gas production in centimeters somewhat more in Period II (Finkelstein) than in Period III (2-7-3). Smears of sediment branched rods (probably bacillus bifidus) present in both foods (greatest number on Finkelstein's food). Many yeasts present in this first test. (Yeasts constantly present in fecal smears in both cases.)

Dextrose.—All tubes showed cloudiness and gas. Average in centimeters greater on Finkelstein's food than on 2-7-3. Most gas produced in this sugar, although only slightly greater than in lactose. Branched organisms

(probably bacillus bifidus) present on both foods, yeasts present on both foods. (Greatest frequency on this sugar.)

Saccharose.—All tubes showed cloudiness and gas. Slightly greater amount in centimeters on Finkelstein's. Least amount of gas produced on this sugar. Branched forms (probably bacillus bifidus) present in all the tests. Yeasts present in considerable amounts on both diets.

$^{8}/_{10}$ *Acetic Acid: Two Per Cent. Dextrose.*—Question of cloudiness on both diets. Small number of bacteria in smear. About the same types constantly present. Various sized Gram positive rods and diplococci and Gram negative rods and diplobacilli present. Yeast very rarely seen.

$^{8}/_{5}$ *Acetic Acid: Two Per Cent. Dextrose.*—Question of cloudiness on 2-7-3 diet. Few bacteria, as a rule, seen in the smears. Occasional yeast present. Gram positive various sized rods, diplococci and diplobacilli, and Gram negative rods and diplobacilli present. Branched and knobbed rods (Gram negative) appeared in Period III in Lizzie's tubes. Spore-bearing rods present in one test of Hazel's in Period III.

Gas Bacillus Test.—Negative on both foods. (B. Welchii.)

(The non-correspondence of the Gram smears of the sediments with each other and with the fecal smears agrees with the findings of Herter and Kendall[7] on this point.)

GENERAL CONCLUSIONS.

(1) The foods used, albuminized milk and simple modified milk (fat, 2 per cent.; sugar, 7 per cent.; proteid, 3 per cent.) had very little influence on the biologic reactions of the fecal flora as a whole. There was, however, a slight lessening of the putrefactive reactions on the 2-7-3 modification. The acidophilic flora remained about constant on both foods.

(2) Finkelstein's food is buttermilk with the salts and sugar reduced and a high percentage of finely divided proteid. To a great degree the beneficial effects of the food depend upon its lactic acid content, and in giving the food we are really using lactic acid therapy. The lactic acid bacillus flora formed during its administration was continued when the food was changed to 2-7-3, because in the latter instance the lactic acid was formed from the sugar. In other words, with both foods lactic acid therapy was given, so that it is not surprising that the bacteriologic reactions were similar in both instances.

(3) In striking contrast to the slight changes in the intestinal flora there was a remarkable change in the clinical aspect of the two cases. The general condition improved greatly, as did the gross character of the stools. On the Finkelstein food there was moderate but steady gain in weight, while on the 2-7-3 modification there was very marked and rapid gain in weight.

(4) The Finkelstein food was undoubtedly of marked value in both these cases. After its administration the gas bacillus disappeared in each case. Again the low sugar content of the food undoubtedly rested the gastrointestinal tract, so that after four weeks of its use an increase of sugar

ad maximum (7 per cent. lactose) was not only tolerated, but utilized with great benefit to the child.

(5) Finkelstein's food is undoubtedly of great value for short periods in suitable cases, for its effect upon the intestinal flora (substitution of acidophilic for putrefactive organisms) and also because of its power to rest the gastrointestinal tract by its low sugar content, especially for cases previously overloaded with sugars.

Our thanks are due to Dr. W. B. Wherry, Professor of Bacteriology, University of Cincinnati, for his helpful suggestions and kind supervision of the bacteriologic work.

REFERENCES.

1. Talbot: Archives of Pediatrics, February, 1911.
2. Kendall: Boston Medical and Surgical Journal, March 2, 1911.
3. Herter: "Bacterial Infections of the Digestive Tract," 1907.
4. Kendall and Smith: Boston Medical and Surgical Journal, March, 1911.
5. Kendall: Journal of Biological Chemistry, 1911, Vol. VI, p. 499.
6. Leopold: Archives of Pediatrics, August, 1910.
7. Herter and Kendall: Journal of Biological Chemistry, 1908-1909, Vol. V, p. 284.

TUMORS OF THE MEDIASTINUM.*

By W. D. Haines, M. D.,

Cincinnati.

The classification of tumors is one of the most changeable and unsatisfactory chapters in surgical pathology; each text-book contains a different classification and each author, like the housewife with her sewing machine, thinks he has the best; there is, however, an encouraging note in the wide discrepancies contained in books published within the quarter of a century just passed, in that with the increase of our knowledge concerning casual factors in the production of tumors there has come a gradual diminution in the number of morbid conditions formerly known as tumors. This better comprehension of production of tumors has resulted in the combining under one head of a number of conditions which were formerly considered as independent. Uppermost in this evolution is the recognition by investigators that tumors are made up of tissues normally present in the human body; i. e., the new growth is but a new arrangement of old structures. This does not imply that the new growth is made up of tissues identical with its immediate surroundings, but that the component parts may be found existing normally in the body—chondromata occurring in glandular tissue, dermoid cysts of the ovary and numerous other examples will come to mind wherein totally unlike "foreign" tissue has been found in tumors, but upon examination we find such foreign tissue exists as such elsewhere in the body, and we leave to the imagination the task of explaining the presence of such tissue in an unusual location.

By far the greater number of intrathoracic tumors are located in the mediastinum, save aneurism, nearly all of them have their origin in the glandular tissue contained in this space. Neoplasms of the chest occurring outsid the mediastinum usually involve these spaces in the course of their development. While it is manifest that the site of the tumor will dominate the clinical manifestations which occompany its development and determine the line of treatment to be instituted, still more importance attaches to determining the true nature of the growth and the effect it will probably produce upon the surrounding structures. The scheme of diagnosis, therefore, should include careful consideration of the early and more or less obscure symptoms embracing muscular pains, irregular heart action, difficulty in breathing or swallowing, spasmodic affections of the laryngeal muscles, and pleuritic irritation and cough with or without effusion.

The following case illustrates some phases or mediastinum tumors.

The patient, a merchant, age 57 years, could not recall having had any serious illness until within the past six months, at which time the present trouble began. He has had to get up once or twice each night for the past four or five years to urinate. Six months ago he weighed 235 pounds, which was about his average weight; to-day

he weighs 170 pounds. Four months ago he began to have a distressing cough, although he could raise nothing from the lungs. He sometimes vomited during the effort, and this was followed by marked relief. Shortness of breath had caused the patient practically to abandon his business affairs. He had taken much medicine including iodides, without benefit. On more careful questioning the patient said he had had pain between the shoulders for a year or more. This was increased after eating or on lying down, and especially made worse by rapid walking or lifting. He could not lie on the left side.

Physical examination revealed a mottled, brownish discoloration of the skin, with prominent veins; the left chest seemed to be slightly fuller than the right, the supraclavicular glands on the left side were large and movable but not tender; there was a slight bulging at the suprasternal notch; light pressure at this point caused an intense coughing seizure, following which the patient was hoarse until after taking a sip of water. There was dullness over the left chest, which extended as high as the sixth interspace with the patient in a sitting posture. This dullness changed with a change in the posture of the patient. Dullness behind the sternum extended a short distance to the right and was continuous with the heart dullness on the left. The breath sounds over this area were absent and they were indistinct over the rest of the left chest below the scapula. The heart action was rapid and irregular, but no valvular disturbance was detected.

Protracted cough and rapid loss of weight had caused my consultant to regard the case as one of tuberculosis, but the absence of fever and the fact that no râles were present, although the disorder had been going on six months, made it seem more probable that some more serious disease was causing the pain, which had been persistent from the beginning.

The apical dullness was readily explained by the presence of the enlarged glands, and the absence of fever and local muscular spasm would rule out a high Pott's thus narrowing the probable limits of diagnosis to two conditions—aneurism or tumor.

The rapidity with which emaciation had taken place (he had lost 60 pounds in six months) caused me to favor malignant growth in the mediastinum as the most probable explanation of the symptoms and physical findings. Fluid aspirated from the left pleural cavity was clear and the X-ray showed a distinct shadow extending from the suprasternal notch downward a distance of 2½ inches and projecting beyond the margins of the bone.

The growth was removed by subperiosteal resection of the inner end of the left clavicle and attached muscles. It was made up of a number of enlarged lymph-glands rather loosely held together. Little difficulty was encountered after exposing the mediastinum, as the mass was shelled out easily by means of the finger and scissors.

There was very little hæmorrhage at the time of operation, and save a troublesome leakage from a large lymph-duct, probably the left jugular, the patient made a smooth recovery and lived two years after the operation, dying of some brain trouble. An autopsy was not obtained. The laboratory reported the growth as a lymph-sarcoma.

Another case may also prove of interest.

A man 55 years old presented a history similar to the foregoing and was *in extremis* when admitted to the hospital. We attempted to remove the growth by the method outlined above, but owing to the intimate attachment of the tumor to the trachea complete removal was impossible. The growth, which sprang from the remains of the thymus, had permeated the entire thickness of the tracheal wall and showed vegetations on the lining surface. The tracheal rings had been destroyed by pressure, permitting the walls to collapse to such a degree as almost to occlude the lumen.

As in the preceding case herein reported, the method of attacking this growth gave a very good exposure, and we succeeded in removing part of the tumor before it became manifest that complete removal would necessitate resecting a segment of the trachea. The patient died within the next 12 hours, and this specimen was removed after death. The growth is a sarcoma.

For our purpose we may arbitrarily divide these growths into benign and malignant tumors, the former group including aneurism, gumma, and tuberculosis, the later including sarcoma and carcinoma. Other morbid growths occur in this region, but the above are the more frequent varieties and all sufficient for consideration in a twenty-minute paper.

Conclusions founded on observations of the natural history of these several growths will best serve us in their early recognition and differential diagnosis. Some of these growths run a much more rapid course than others; some present marked constitutional symptoms and serious impairment of the general health long before symptoms referable to the chest manifest themselves.

Recognition, therefore, of the wide difference in the general aspect and progress of intrathoracic growths, aside from the special features which in no small measure characterize each case, becomes paramount in the diagnosis, prognosis, and management of these growths. Malignant growths, for instance, as a rule grow much more rapidly than the benign ones, destroying life in from 12 to 18 months. A notable exception to this rule is found in lymphosarcomata springing from the posterior mediastinal glands or remains of the thymus. Such tumors may attain an enormous size and the patient live a long time, death finally resulting in consequence of metastases.

Growths springing from the connective tissue in the mediastinum—sarcomata—may attain considerable size without producing symptoms, this being due to the laxity of the tissue and the ease with which enlargement may take place in all directions. To the writer's mind this is a valuable point to remember in attempts at localization of chest tumors. The site of the aneurism is more or less fixed, and you will recall that it is in this type of case that we encounter those enormous deformities of the chest, including bulging, erosion, and fracture of the bony cage. Extensive deformity occurring relatively early in the history of intrathoracic neoplasms may be induced by implication of a bronchus, which causes collapse of the corresponding lung and compensatory expansion of the opposite side. Derangements of the circulation are constant concomitants of mediastinal tumors: they are caused, not alone by external pressure upon the vessel walls, but also by the inherent tendency of sarcomata to permeate the walls of the veins, thereby inducing partial or complete occlusion and metastases. The effects are manifold, finding expression in œdema, metastases, hæmorrhagic effusions into the pleura, pulmonary and cerebral apoplexy, gangrene, and death.

Although functional disorders of the heart with modified rhythm and sounds, without discernible valvular or muscular impairment, are the usual findings, cases are recorded in the literature wherein the heart has been involved in a similar manner to those rare cases of malignant breast in which the disease, by extending through the thoracic wall, affected the heart. Pain in some degree is usually present, but the chief complaint of th patient suffering of mediastinal tumor will be of his inability to get his breath; the pain, cough, and aphonia are annoying, but the dyspnœa is persistent and terrifying, filling the patient's mind with ominous forebodings. This, the most prominent of the subjective symptoms, is characterized by a wide discrepancy between the amount of exercise and the respiratory disturbance;

for instance, the writer has seen a patient, the subject of a mediastinal growth, who had been sitting in perfect comfort, bring on by merely walking across the room a violent spasmodic coughing seizure and serious respiratory embarrassment.

From what has been said it becomes apparent that no one sign or symptom or hitherto described order of phenomena can be said to be pathognomonic of a certain intrathoracic growth. The cases vary widely, but by eliminating the ordinary forms of disease in a patient suffering of serious derangement of the mechanics of the chest, one is warranted in making a presumptive diagnosis of mediastinal tumor.

In the differential diagnosis aneurism stands out preëminently for first consideration. The physical signs of aneurism comprise a loud murmur or splashing sound, accompanied by a purring thrill, which is imparted to the hand of the examiner when placed on the chest, and interference with arterial circulation, delay, feebleness, or absence of the radial, brachial, or carotid pulse. Interference with the return flow is common to both aneurism and solid tumors, occurring much earlier in the history of the latter than in the former.

Retardation of the radical pulse on one side may be observed in cases where an aneurism is situated distal to the origin of the great vessels given off by the aorta. Sphygmographic tracings are of signal value in the differential, and comparative tracings should greatly aid one in definitely fixing the site of the aneurism.

Symptoms dependent upon pressure manifest themselves later in aneurism than in other growths, but, aside from this, possess no particular difference which would serve as aids in the diagnosis. The physical signs of aneurism, like those of other intrathoracic growths, will vary with the time of observation; if the subject of an aneurism presents himself at a time when there is a considerable degree of elasticity in the sac-wall and, above all, at a time when fluid contents fill the sac, the classical expansible tumor, peculiar vibratory thrill, and loud tumultuous sounds render diagnosis easy; quite different, however, are the signs after layer upon layer of clots are deposited upon the inner surface of the sac. Instead of a resilient sac we now have to deal with a thick, rigid wall which limits the production of sounds, interferes with their transmission to the ear of the examiner, and presents the characteristics of a solid tumor.

Although sarcoma is the prevailing type of malignant tumor found in the mediastinum, carcinomata are found sufficiently often to enable us to summarize their leading clinical features. Primary carcinoma in this region has, in the writer's experience, more frequently begun in the gullet than elsewhere, and the symptoms are those of a slowly but steadily increasing difficulty in swallowing; solids are first discarded and in the course of a few months the patient rapidly succumbs if not relieved by surgical measures.

Sarcomata in their early history are painless and increase in size slowly. Owing to these facts the patient does not present himself until pressure symptoms—cough, hoarseness, or dyspnœa—drive him to seek council.

Rapidly growing tumors, like gummata, are painful very early in their course, and pressure symptoms, irregular pupil, aphonia, and dilated surface veins and serious right heart embarrassment soon follow. Growths in the anterior and superior mediastinum are in a measure distinguished by pressure exerted by them upon the superior cava and innominate, while interference with the inferior cava or azygos would suggest the presence of a tumor in the posterior mediastinum. Implication of the venous circulation, ciliomotor roots of the sympathetic, recurrent laryngeal or pneumogastric, relatively early in the history, speak for solid tumor as contrasted with aneurism, which always shows symptoms on the part of the arterial circulation long before venous stasis becomes manifest.

Tuberculous adenitis, leading to caseation and abscess, affect this region, and the enlarged glands must be differentiated from other growths. This condition, like gumma, is ordinarily not difficult of recognition, as in either instance we are dealing with the local expression of a disease which has almost innumerable general symptoms, a sufficient number of which are usually present preceding the central chest lesion to readily distinguish them from other conditions found in the mediastinum. Finally, we possess valuable therapeutic tests which will aid in the differential diagnosis of both tuberculous and luetic growths.

Patients dead of sarcoma of the mediastinum are singularly free from metastases. Money, an English pathologist, posted a number of bodies in which the disease was wholly confined to the mediastinum, and the writer's experience in the dead room tends to confirm this view. If this observation proves true in any considerable proportion of the cases of sarcoma originating in the mediastinum, it should encourage surgeons in their efforts to relieve, by operation, a condition which has hitherto been regarded as well-nigh hopeless.

Numerous methods have been devised for exposing the anterior and superior mediastial spaces; they include trephining, osteoplastic flap, and longitudinal division of the sternum; these and other operative procedures were devised with a view to dealing with aneurisms.

Bardenheuer separated the muscles subperiosteally from the clavicles and manubrium, and then by dividing the clavicle and first rib on one side he was able to remove a growth from the mediastinum. The writer has employed this method in two instances, and while a fair exposure of the field is obtained, there are certain obstacles which should be regarded before attempting the operation. The chief objection lies in the liability of injury to the pleura. Damage done to the circulation in the course of the operation renders the field more susceptible to infection, and lastly the operation is technically difficult.

The operation devised by Milton for exposing the mediastinum is less complicated and free from these objections, and it gives a more satisfactory exposure of the field for operation. He divided the sternum longitudinally throughout its entire length in order to remove a foreign body from the right bronchus, which he successfully accomplished.

American surgeons, notably Curtis, with a view to avoiding injury to the pleura have modified the operation by limiting the division to the manubrium, at which point the pleura is widely separated.

As modified the procedure consists of an incision which is carried from the larynx downward in the midline to a point opposite the third interspace. The sternohyoid and the sternomastoi muscles are detached subperiosteally and are well retracted while the manubrium is being divided longitudinally. In sawing through the bone the saw should discontinue on reaching the periosteum covering the posterior surface and a chisel should be inserted to pry the severed margins apart. This enables one to divide the periosteum safely under the guidance of the eye.

Mayo's blunt pointed scissors are well adapted for dividing the periosteum. The margins of the divided bone may be retracted two or two and one-half inches, permitting the free introduction of instruments and fingers. In doing the operation the chief structures to be avoided are the pleura and the internal mammary or its branches. Division of the latter will cause hæmorrhage, which is difficult to control.

The writer's experience with the Milton operation has been limited to the cadaver. However, the exposure obtained by this method will permit one to ligate the innominate, carotid, or subclavian and deal with operable neoplasms in this region.

REFERENCES

Da Costa Physical Diagnosis.   Flint Practice of Medicine.   Cabot Differential Diagnosis.

A STRIKING ELEVATION OF THE TEMPERATURE OF THE HAND AND FOREARM FOLLOWING THE EXCISION OF A SUBCLAVIAN ANEURISM AND LIGATIONS OF THE LEFT SUBCLAVIAN AND AXILLARY ARTERIES.*

By William S. Halsted

In a series of signally interesting papers Professor René Leriche calls attention to the value of what he terms periarterial sympathectomy in the treatment of various neuralgias, local ischemias, reflex contractures of the Babinski-Froment type, and other affections. Fostered in the traditions of the schools of Magendie, Claude Bernard, and Brown Séquard, it was in the happy order of things that it should fall to the lot of a surgeon of Lyon to turn to therapeutic account a discovery of the greatest of the founders of experimental medicine. A devoted disciple of Jaboulay, Leriche credits this talented surgeon, his "master," with the suggestion which led to the novel and important researches made by him during the years of the war.

My interest in Leriche's work has been reawakened by an observation made only a few weeks ago in the Surgical Clinic of The Johns Hopkins University. In 1918 I ligated the left subclavian and carotid arteries near their origin from the aorta for the cure of a huge subclavian aneurism (Figs. 1 and 2). For a year the aneurism decreased steadily in size (Figs. 3, 4, 5 and 6). Then for a year we lost track of the patient. About two months ago we succeeded in tracing him, and persuaded him to let us excise the aneurism, which in the period of non-observation had developed a faint pulsation and become slightly larger (Fig. 7). About four hours after this operation, at which the aneurism was excised and the subclavian and axillary arteries ligated, it was noticed that the left hand and forearm, which for two years had been strikingly cold, had become abnormally warm—appreciably warmer than the corresponding limb. Unfortunately, our surface thermometer had been broken and we were unable to obtain another. About five weeks after the operation the hand and forearm became cold again—at first in small areas—remaining cold for only a day or two.

To-day (June 28) the 69th since the operation, the back of the left hand is quite cold, whereas the left palm is about as warm as the right. The temperature of the hand and forearm has varied from day to day and from hour to hour; certain small, quite well-defined areas have remained uniformly cool; otherwise, the hand and forearm have maintained their normal warmth.

Surg. No 46179. Alexander Miller. Negro; æt 29. Admitted to The Johns Hopkins Hospital April 22, 1918; discharged August 12, 1918.

The patient states that he has always been perfectly well. In April, 1917, he noticed a swelling about the size of an egg above the left clavicle. Almost simultaneously with the recognition of the swelling, pain and numbness in the upper extremity were observed. The growth of the tumor was gradual until about March, 1918; since then it has been very rapid. For the past two weeks the limb has been totally paralyzed. The patient recalls that until Christmas, 1917, he could still raise his arm a little.
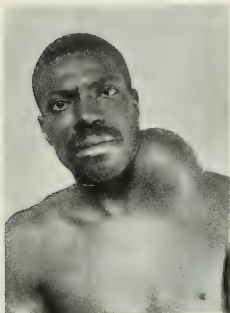
Fig. 1.—Aneurism of the left sub-
clavian artery,
Alexander Miller, April 22, 1918.
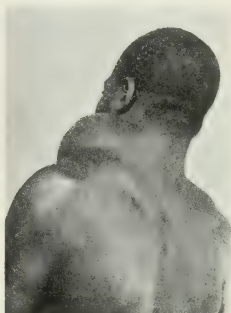
Fig. 2.
Alexander Miller, April 22, 1918.

Fig. 3.—Alexander Miller, 109 days
after ligation of the subclavian artery
nuear its origin.
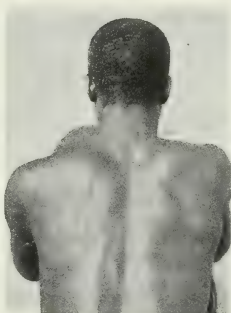
Fig. 4.—Alexander Miller, 109 days
after the ligation.

Plate LII
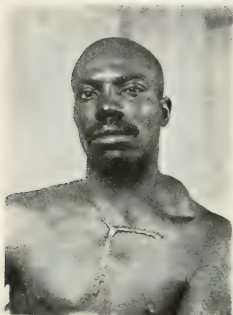
Fig. 5.—Alexander Miller, 10 months after the ligation.

Fig. 6.—Alexander Miller, 10 months after the ligation.
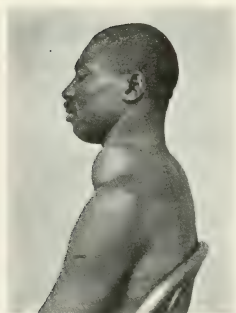
Fig. 7.—Alexander Miller, 2 years after the ligation of the subclavian, and 2 weeks before the excision of the aneurism.
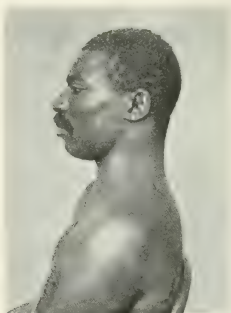
Fig. 8.—Alexander Miller, 1 month after excision of the aneurism.

About four years before admission the patient was shot just above the left clavicle. The wound healed promptly. The bullet was not removed and has given him no indication of its presence.

Examination.—The patient is evidently suffering severe pain, and constantly supports his left wrist with his right hand. The pain, he says, is most intense from the elbow-joint to the hand and in the left shoulder.

A huge aneurism occupies the left neck from the clavicle to the ear (Figs. 1 and 2). The head is deflected and rotated to the right. The vertex of the pulsating mass is about on a plumb-line dropped to the junction of the middle and inner thirds of the clavicle. The swelling and pulsation extend on to the chest, and the whole body is jarred with each heartbeat. Posteriorly the diffuse pulsating tumefaction spreads out to a point below the spine of the scapula. The aneurism extends upward in domeshape; a hand can be inserted between it and the face down to the angle of the lower jaw. The whole shoulder girdle appears to be raised away from the chest wall, the acromio-clavicular articulation being apparently disrupted. The skin over the tumor is very tense and glistening. From the clavicle to about the level of the nipple the brawny tissues are probably infiltrated with blood as well as inflammatory products. The trachea is displaced to the right. A systolic bruit, most distinct above the inner third of the clavicle, can be heard over the greater part of the pulsating mass. No thrill can be felt. The left radial pulse is absent. There is slight ptosis of the left eyelid, but the pupils respond equally. Only the inner third and the acromial tip of the clavicle can be defined with the fingers. The remainder of the bone is buried in the tumefaction. A bullet is palpable just beneath the skin to the left and below the spine of the seventh cervical vertebra. The left arm is paralyzed. The extent of the loss of motion and sensation and the degree of restoration of function will be outlined in a subsequent paper.

Fluroscopic Examination.—The shadow of the aneurism extends to the lower border of the clavicle but not to the first rib. The heart seems not to be enlarged. The right subclavian and carotid arteries, distinctly seen, are normal in size.

Skiagraphic Report.—Large mass in left neck. Clavicle deeply eroded, perhaps fragmented. Bullet in upper dorsal region.

Operation.—April 26, 1918. Dr. Halsted. *Ligation of the left common carotid and the left subclavin arteries near their origin from the aorta.*

Ether. Wide protection of the operative field with celloidin-silk.[1] Transverse bow-incision just below the cervico-thoracic junction, supplemented by a vertical one along the left border of the sternum (bow and plummet incision). Free exposure of manubrium and left sterno-clavicular joint. The incised tissues were œdematous, particularly so below the clavicle. The superficial vessels were abnormally large. Careful hemostasis by the fine silk transfixion method. The left two-thirds of the manubrium and the left sterno-clavicular joint were resected with the giant rongeur forceps of Esmarch, care being taken to avoid disturbing the fragments of the eroded clavicle. The thymus gland and the left innominate vein were drawn upward and to the right with a retractor.

The trachea in the thorax as well as in the neck was displaced to the right by the pressure of the aneurism. The left carotid, deeply situated and occupying the midline in the chest, was gently occluded with a tape ligature. This artery was thought at first to be the left subclavin inasmuch as, according to the erroneous testimony of an assistant, its occlusion did not affect the pulse in the left temporal artery, and lessened the force of the pulsation in the aneurism. To obtain access to the left subclavin artery the cartilage of the left first rib and the adjoining margain of the sternum were cut away. The arch, the aortic isthmus and descending oarta, and the left auricle of the heart were palpated with the finger of the opeartor before the left subclavian, lying close to the vertebral column, was identified. With the aid of four long, narrow dissectors, two of which were manipulated by the operator and two by Dr. Mont Reid, the vessel was clearly exposed at its origin from the aorta and for several centimeters distal to this point. As it was evident that none of the various aneurism needles was suitable for the passage of a ligature at this depth, a long, narrow, blunt dissector, slightly curved and pierced at its tip, was armed with fine silk and passed under the artery. By means of this thread and then another, linen tapes were drawn under the subclavin; both of these were tied, the second distal and close to the first, with force only sufficient to close completely the artery's lumen. The aneurism became very tense and hard immediately after the ligation, but was pulseless.

The patient's condition, bad on admission and particularly so just before operation, caused us some anxiety. Traction within the thorax on the branches of the aortic arch or on the pulmonary artery affects unfavorably and eventually disastrously the

action of the heart. The pulse, about 120 at the beginning, was 140+ and quite weak at the termination of the operation. The wound was completely and accurately closed with interrupted sutures of fine silk. A large dead space in the mediastinum was, naturally, unavoidable.

Healing *per primam*.

November 9, 1918. The patient has been examined frequently since his discharge from the hospital. There has been no pulsation in the aneurism since the operation. The mass has steadily but slowly decreased in size. The patient can make slight movements with the left fingers, otherwise there has been no appreciable return of power or sensation in the paralyzed arm.

The patient was observed frequently throughout the year following the operation. Slowly but steadily the pulseless tumor, during this period, diminished in size. Then for a year the patient, living out of town, was lost sight of. Exactly two years after the first operation he returned, at our solicitation, to the hospital. Now for the first time since the operation a very faint pulsation was discernible. The tumor (Fig. 7) measured in its transverse (frontal) diameter precisely the same as when last seen a year before; the anteroposterior measurement (sagittal), however, gave an increase of about 4 cm. I decided that the aneurism should be excised, and on the 20th of April, 1920, performed the operation as follows:

The skin over the tumor and a wide area about it were protected with Chinese silk dipped in colloidin. The incision, made through the tightly adherent silk, ran with the clavicle in its central part, curving up into the neck at its inner end, and down along the cephalic vein at its outer. Superimposed on and not attached to the greatly broadened and thickened clavicle was a sharply convex bow of bone about 9 cm. long and 6 mm. thick. This bow, recognizable in the photograph (Fig. 5), was cut away and the clavicle bitten through with a heavy rongeur forceps at two points as close to the aneurism as possible. The cephalic vein was divided, and the axillary artery—pulseless, reduced in size, but not empty—was ligated about at the junction of its first and second portions, through a split made in the pectoralis minor muscle; the third portion of the subclavian artery was ligated above the clavicle; the aneurismal sac, and the resected rib were excised in one piece. The aneurism was matted almost everywhere to the surrounding parts by dense connective tissue, and hence had to be carved out rather than enucleated. The identification and freeing of the roots of the brachial plexus, which were in places embedded in the wall of the sac, consumed much time. The operation was conducted in a bloodless manner until nothing remained to be done except to divide the narrow neck of the sac. The tissues of this neck proved to be thin and friable, and the patient lost a few cubic centimeters of blood through the slit in the artery—the mouth of the false sac—which was readily closed with three stitches of fine silk. The wound was closed without drainage. I am greatly indebted to Dr. Heuer and Dr. Reid for their skilful and highly competent assistance which enabled me without concern to conduct the operation to a satisfactory conclusion.

At the first dressing, made on the 10th day after operation, it was noted that a little fluid had accumulated in the outer part of the wound. This was evacuated by puncture with a wooden toothpick wrapped with a few fibres of cotton dipped in pure carbolic acid. Closure of the puncture was prevented by the reapplication of the acid in the same manner on two alternate days. The introduction of a drain of any kind we scrupulously avoid. The word "drainage tube" is in disfavor in our clinic. Should a wound become infected, tubes would be properly introduced for the purpose of disinfection, but not for drainage.

Noteworthy is the fact that the patient's hand and forearm, which prior to and ever since the first operation had been markedly cold, became strikingly warm about four hours after the second operation and have remained warm, except in certain areas, to the present time (June 28). It is improbable that the ligation of the cephalic vein was in any part responsible for this indubitable improvement in the circulation. The elevation of the temperature of the hand and forearm must, I believe, be attributable to vasodilatation

incident to the ligations of the subclavian and axillary arteries—to the crushing of their nerves. This question will be discussed in the course of the consideration of the treatment of subclavian aneurisms in a paper about to appear in The Johns Hopkins Hospital Reports.

I have found pleasure in translating one of the papers of Monsieur Leriche, believing that his work on periarterial sympathectomy will at this moment particularly interest surgeons who may have the opportunities and the inclination to verify his observations. While disclaiming unqualified acceptance of some of his explanations and deductions which are at variance with the teachings of physiologists we must recognize that Leriche's contributions are of unusual interest and value; they will stimulate investigation.

PERIARTERIAL SYMPATHECTOMY AND ITS RESULTS
Rene Leriche

In January, 1916, and in April of the same year,[2] I made known the first results which the denudation and excision of the sympathetic plexuses around the arteries in causalgia and in certain trophic troubles had given me. Since then this operation has been tried in various ways. Le Fort, Cotte, Sencert, Lavenant, de Massary and Veau, Prat, have reported experiences with it. I personally have performed it 37 times[3] The moment seems to have come to indicate briefly the essential facts which the procedure has taught me. Elaborating the idea of Jaboulay, we must indeed develop a true and general operative method susceptible of very varied applications.

I think at the outset that it ought to be designated by an exact name: it is a peripheral sympathectomy which, according to the level where it is practiced, ought to be called axillary sympathectomy, brachial, iliac, femoral, etc.

I. TECHNIQUE.—In order to achieve it, it is necessary to uncover the artery by the classic procedure, open with the bistory the cellular sheath, separate the artery for 8 to 10 cm., get hold of the inner sheath directly on the vessel wall, incise it, and pull one of the lips thus made with a forceps, free it either with the bistory or with the grooved probe, completely stripping the artery of all the cellular tissue that adheres to it. More or less easily according to the cases, one is able thus to strip the artery, to decorticate a fold; thin, to be sure, but often thicker than one might expect. At a certain moment one has the impression that one is going to tear the wall of the artery; but if one proceeds gently and carefully, guided by the point of the bistory or probe, the freeing process can be carried on without risk of injuring the vessel. Only twice have I had the annoyance of making a small tear in the artery; the accident was without serious results. In case of necessity one would frankly resect the segment of the tear and tie the two ends, accomplishing thus by the same act a complete sympathectomy. Sometimes the forceps removes only rather short cellular fragments, at other times one removes quite definite laminæ, and the movement of freeing recalls, on a small scale, the subserous decortication of an inflamed appendix, but one never succeeds in removing a continuous layer; it is necessary to repeat the attempt several times and with perseverance to catch the sheath again, to remove thin meshes, and not to stop until one has really the feeling of having removed everything. Moreover, one can verify what has been done by wetting the wound with a tampon soaked with very warm serum: the artery takes on then a whitish appearance, looks as though made of felt, and one sees very clearly whether there remains still some cellular débris more or less detached.

In the course of the cellular decortication it is necessary to be careful to expose the collateral branches and guard against tearing them. This happens sometimes; by using then a forceps and a   ¿ ,gut one repairs this accident without injury to the artery. In addition to the tears, which cause a spurt of pure blood, there may be oozing from the tearing of the vasa vasorum.

II. THE PHYSIOLOGICAL REACTION.—The operation thus done is a physiological operation; I mean to say by this that it is inevitably followed by a characteristic physiological reaction, which may be regarded as the *test of the operation;* as there are char-

[2] R. Leriche: De la causalgie envisagée comme une nevrite du sympathetique et de son traitement par la denudation et l'excision des plexus nerveux peri arteriels. Société de Neurologie, 6 Janvier 1916; La Presse medicale, 20 Avril 1916.

[3] More exactly, I have done 30 sympathectomies by denudation and 7 times complete sympathectomy by resection of a segment of obliterated artery.

acteristic signs of the section of the trunk of the sympathetic in the neck, so there are characteristic signs of the section of the periarterial sympathetic nerves. If these are wanting, the operation has been attempted but not accomplished.

The results of our studies of these signs Heitz and I have reported to the Société de Biologie;[4] they are as follows:

Primary Sign.—When one touches the sympathetic sheath, the artery contracts; it is reduced progressively in size to the point where it is not more than a third or even a fourth the normal size throughout the whole extent of the denuded segment. The segments on both sides maintain their normal size provided the operation has not injured them. The phenomenon is more or less rapid according to the case: certain individuals appear to have more irritable sympathetic nerves than others; their arteries diminish in size at the first touch; with some the contraction is sluggish. One cannot yet give the real reason for these variations. Furthermore, the contraction is more marked in the brachial than in the axillary and the subclavian; it is slower in the femoral than in the brachial, and less intense in the common iliac than in the femoral. In a word, the contraction is stronger in the arteries of small size than in the large trunks.

This arterial contraction habitually causes the pulse to disappear, but it does not altogether interrupt the circulation.

Secondary Signs.—In the following hours the pulse is imperceptible or very feeble and the limb is colder than the other. Then little by little, at the end of three hours, six hours, and most often after twelve or fifteen hours there appears the *characteristic physiological reaction,* the establishing of which ought to be exacted as proof that suppression of the sympathetic nerves has been properly done.

This reaction is characterized by an elevation of the local temperature reaching to 2° and even 3° [centigrade], by the elevation of the arterial pressure, and by the augmentation in the amplitude of the oscillations of Pachon. M. Heitz, who with his very special competence has established these facts many times on my patients, has found that the increase in pressure could be as much as 4 cm. of mercury in comparison with the healthy side (method of Riva Rocci); it is a detail worthy of mention that analogous figures were noted by Claude Bernard in his investigations of the cervical sympathetic nerves.

This vasodilator reaction is only temporary; the hyperthermia, the rise in pressure, and the increase in amplitude of the oscillations diminish little by little; sometimes as early as the 15th day and usually at the end of a month one finds it no more. On the other hand, in some cases in which I have performed sympathectomy on the brachial or the subclavian artery by resecting totally the obliterated arterial cord, the elevations of temperature have been more lasting than in the cases in which a sympathectomy by denudation alone was done. This is comprehensible, for the operation is more complete—the sympathectomy being necessarily total. Classed with these observations should be one made by M. Babinski and M. Heitz: four months after the extirpation of an axillary aneurism the hand on the side operated on was frequently warmer than that on the healthy side. This phenomenon, apparently paradoxical, is understood very well when one considers that the ablation of a sac is in reality a total sympathectomy.

III. The Lessons Furnished by the Operation.—Observation of series of operations and analysis of the therapeutic results permit interesting deductions from physiological and pathological points of view.

1. *From the Physiological Point of View.*—Two facts become clear: the vasomotor phenomena which Heitz and I have studied under the name of vasodilator reaction permit us to isolate the paths along which certain vasoconstrictive acts are conducted and to establish their correct value.

But there is, above all, this one: it seems to follow from certain observations that the voluntary muscular contraction is, in a certain sense, very dependent on the sympathetic nerves. The integrity of the motor nerve and of the muscle are not sufficient to insure the proper accomplishment of the movement that is commanded. If the sympathetic nerve is affected at a distance, or if it does not act normally, the muscle becomes hard, and contracts, and the will is powerless to relax or contract it. Now in these cases sympathectomy lifts the barrier and makes possible the progressive reparation of the voluntary movements. In the case of wounded men having reflex contractions of the Babinski-Froment type, with fingers twisted, motionless, incapable of movement, it has been sufficient to modify the vasomotor innervation to see a certain degree of voluntary motion appear again the following day.

This fact which M. Heitz[5] and I have confirmed several times has a real

[4] [illegible French footnote text] Heitz [illegible] sympathetiques periphériques [illegible] locales). [illegible] R [illegible] S [illegible] B [illegible] Lavaur [illegible]

[5] [illegible French footnote text] Heitz [illegible] Influence [illegible] le sympathique periarteriel [illegible] sur la contraction volontaire des muscles. Société de Biologie, 17 [illegible] 1917

physiological Learing. What we now know of muscle innervation in man does not lead us to suppose that it is a matter of a directly muscular action. It appears, until we have made further inquiry, that the vasomotor phenomena alone are concerned in it, and a fact which would tend to prove this is that the return of motility coincides with the appearance of the post-operative vasodilator reaction (that is to say, the warming up of the muscle, its new circulatory system), and follows the course of it.

Sympathectomy, furthermore, would appear to establish the fact that the sympathetic nerve is, in man, the excitosecretory nerve of the sweat glands; I have seen profuse sweating of the hand disappear after sympathectomy. The nerve probably also influences the growth of the nails and the trophicity of the skin, since trophic phenomena disappear rapidly after sympathectomy. The nerves of the cerebrospinal system, from this point of view are probably only the vectors of the sympathetic.

2. From the Point of View of Pathological Physiology. Sympathectomy is, in certain cases, a true method of experimental analysis for the interpretation of certain complex phenomena.

It demonstrates: (a) *The true mechanism of the production of dry wounds of the arteries.* Spontaneous hemostasis, when an artery is divided or destroyed by a projectile, is certainly greatly facilitated by, if it is not entirely due to, the contraction of the artery which follows the destruction of its sympathetic nerve. It may be compared to the considerable diminution of calibre which is observed after sympathectomy. Since a brachial artery is reduced to the size of a radio-palmar or a digital when its sympathetic nerve is excised, it is easy to comprehend how spontaneous hemostasis is possible after certain wounds of the arteries which are inevitably accompanied by tearing of the sheath.

(b) *The real nature of certain causalgias, if not of all.* As I demonstrated to the Société de Neurologie, in January, 1916, one can cure obstinate causalgias by excising the involved sympathetic nerve. This observation proves the sympathetic origin of the violent pains which accompany certain wounds of nerves. In these cases the pain phenomena are not due to the nerve lesions, but to the lesions of the neighboring sympathetic nerve (the perivascular sympathetic of the brachial) or of the intra-nerve sympathetic (the sympathetic carried to the median, for example, by its paracular artery). This explains the fact demonstrated by M. Pierre Marie, M. Miège and Mme. Bénisty that the pain in these nerve wounds is a kind of reaction peculiar to the nerves which have an artery of their own or which are close to a large artery. This fact is now admitted by the neurologists.

(c) *The very great role of the sympathetic in the production of the reflex contractions of Babinski-Froment.* Let us pay attention to the characteristics of this type about which there is so much confusion. I speak now of the true Babinski-Froment type, that in which the vasomotor and thermic phenomena are associated with motor disturbances and with modifications of the mechanical excitability of the muscles.

In the cases of this kind, studied by M. Babinski or by his assistants, Froment and Heitz, I have seen with Heitz motor disturbances disappear almost completely after sympathectomy. From the day following the operation, when the vasodilator reaction was very well established, the mobility returned markedly in hands fixed immutably in position, contracted, the fingers being bent into the palms, or else turned back on the dorsal side. I am inclined to believe that a number of these severe cases are referable to disturbances of sympathetic origin, caused by the imprisonment of the nerve ends in a hard and compressing cicatrix.

(d) *The role of the sympathetic in the production of certain griffes cubitales.* After brachial sympathectomy I have seen a loosening up of a very rigid griffe cubitale which had resisted resection and suture of the nerve divided in the forearm.

I have made this observation only once, but the phenomenon was perfectly definite. It seems to me that the observation should be recorded because of its therapeutic interest.

(e) *The role of the sympathetic in the explanation of those motor paralysis, more or less complete, which follow certain arterial lesions.* When the nerves have not been disturbed, we call it ischemic paralysis, giving to this appellation an entirely different sense from that which we have in mind for the isolated contracture of the flexors of Volkmann. In the cases described by MM. Dejerine and Tinel there is rather complete motor paralysis with the reaction of degeneration, yet the nerves were not divided. The paralysis coincides with an œdematous infiltration of the hand with marked vasomotor disturbances which lead to true fibrous transformation of the hand. At the end of some weeks the œdema begins to diminish, the tendons and the aponeuroses are ensheated in a veritable fibrous envelope; the muscles, already hard and tense, retract and take on a ligneous consistency. In this picture is seen the mark of the sympathetic; and in doing sympathectomy in these cases M. Heitz and I have

seen vasomotor disturbances disappear, trophic disturbances improve, the tendons and the muscles become on palpation sensibly more supple, and the muscles execute slight movements. In one case, although before operation there had been complete degenerative reaction, four months after operation we observed a very definite amelioration of the electric reactions, and we are hoping for a marked functional recuperation.

I do not wish to say that sympathectomy cures the patients; and it is impossible that it should cure them at once when one considers their wounds. Unhappily, there is no cure, but to me it appears to have caused the disappearance (at least momentarily) of the stiffness of the muscles and tendons; it has assured a manifest supplying up of muscles which, after the sympathectomy, executed movements equivalent to one-half the normal. Referring to the fact mentioned above á propos of *griffe cubitale*, I have the impression that the sympathetic has an enormous influence on the evolution and production of fibrous tissue. The sclerous evolution is modified, it appears, when a vasodilator reaction is brought about. Whence the conclusion that the sympathetic plays probably a large role in the mechanism of the so-called ischemic paralysis where the predominating feature has not the mark of ischemia. I do not mean to say that the circulatory suppression caused by the arterial lesion does not play any part, that would be absurd; what I would say is that something more is involved. But these cases are too rare in general surgical practice for me to follow the analysis alone.

(1) *The role of the sympathetic in the production of heel sloughs in the course of medullary lesions.* In one patient who had had flabby incomplete paralysis of the lower limbs with absence of reflexes, and incontinence of urine, there were two sloughs, one on the heel, the other on the little toe. They resisted all treatment. Three months after the wound had been received, a femoral sympathectomy was done. Three days later the ulceration of the toe was dry and cicatrized; that of the heel, which was as large as a small palm of the hand, diminished in size and was covered with active granulations. In thirty-five days it was completely cicatrized.

3. *From the Therapeutic Point of View.*—I have tried sympathectomy in a great variety of cases, and it is rather difficult for me to analyse the results, because there were often complex situations to be dealt with. Schematically, I have tried to influence the element of pain, the element of reflex contraction with vasomotor disturbances, and the trophic element. In all the cases I have had failures and disappointments.

I have done sympathectomy eleven times for phenomena of pain; once the vasodilator reaction failed. This operation was badly done and I eliminate it. For the ten others, six times there were true causalgias, and three times phenomena of pain more or less intense.

For *causalgia* I operated four times on the upper extremity, twice on the lower limb. The four cases in the upper extremity resulted as follows: One complete failure (patient operated on in the service of M. Gosset), two excellent results (complete suppression of the pains, total transformation of the patients) with final cure, now dating back 19 and 16 months. These two patients have been discharged, and are earning their living exclusively by their own work.

In a fourth case, which was very serious, I had found the brachial artery obliterated. I had not at the time thought that there would be any advantage in resecting the obliterated segment. I performed then a sympathecomy by denudation The patient was much improved; he who for months had been confined to his bed with a wet cloth on his hand, apprehensive, indifferent to everything except his pain, got up and submitted to the same régime as his comrades; but some pains persisted. In order to improve these I again took the patient under my care and resected the obliterated arterial segment, whereupon the persisting disturbances almost completely vanished; this result promises to be permanent.[6]

In the lower limb I did one femoral sympathectomy, with appreciable amelioration. At a second operation I resected the sciatic artery and the artery of the sciatic nerve, with manifest result, but the cure has not been complete. The patient, who has been followed for six months, is entirely relieved at certain times, but has suffered much at others in damp weather. His general condition is transformed. For those who know the lamentable condition of degeneration of these patients caused by their martyrdom of pain, the words "great amelioration" have a real significance. This expression should not be taken as a euphemism masking a failure.

In another case I did a common iliac sympathectomy, which resulted in great improvement [grande amélioration] with complete transformation of the general condition. The patient has suffered at certain times, but his days of respite have been greater in number than his days of pain. This is also, to my thinking, a success worth trying for.

For all "causalgiques" the question is complex in other ways: these patients have a psychology of their own; it is necessary to isolate them somewhat and to exercise over them a little authority if we desire to cure them. Besides, they are extremely sensitive to atmospheric changes, and it seems as if their whole vasomotor system were out of equilibrium. One local operation could not pretend to set all this right at once, and these patients should not be regarded exactly as others.

I have operated *four times for phenomena of pain accompanying nerve lesions* or arterial obliterations. I had three excellent results and one complete failure.

To sum up, in the treatment of the phenomena of pain, sympathectomy cures entirely certain patients, acts very favorably in the majority of cases, but does not succeed always or always give an absolutely perfect result.

Five sympathectomies for *trophic ulcerations*, with or without phlyctenæ in the neighborhood, gave success five times.

I have operated three times for large *bluish oedemas* of the limbs, with one complete success; one great improvement, followed at the end of several months by complete cure; one incomplete result with partial return (in the lower limb), but on the whole, amelioration.

For reflex disturbances, eighteen sympathectomies among the patients examined heretofore (except two) either by M. Babinski, or by his assistants M. Froment and M. Heitz, and all followed up by M. Heitz, have resulted as follows :[7]

Three cures, practically complete, traced for several months, with disappearance of the vasomotor disturbances and of the contraction ;

Ten ameliorations more or less considerable, some of which were almost cures ;

Two ameliorations followed by incomplete return in patients who had not received any post-operative treatment. In the two cases the lasting benefit has been real ;

One case in which the operation, after failure of all other treatments, has been followed by the execution of voluntary movements ; also, thanks to treatment followed regularly under the direction of M. Heitz, mobility is returning little by little ;

Two complete failures. In these two patients there had been after operation a beginning return of voluntary motility, but the therapeutic result has been practically nil.

In all the patients who have been really benefited by the operation (16) the vasodilator reaction has been followed by a diminution of the contraction and by a reappearance more or less complete of the voluntary movements. In some cases the result has been surprising: from the day following operation the patients were able to make movements which had been impossible for months. But at the end of two or three weeks, as the vasodilator reaction subsided, the contraction shows signs of beginning anew and the movements diminish in amplitude. Observing this, we thought, with M. Heitz, that the maintenance of heat in the member operated upon was indicated. For this purpose M. Heitz has made my patients take baths of paraffine at 60° for about one half hour. By associating with this treatment massage and re-education Heitz has obtained very interesting results, which permit us to speak, in certain cases, of true cure.

Briefly then, *in the grave forms of the syndrome of Babinski-Froment* sympathectomy by itself does not suffice. But without it, the treatment usually applied soon ceases to influence the condition, and the result becomes stabilized; the operation, like so many other operations upon the nervous system, leaves room for and facilitates re-education, and gives to it its efficacy. It is only one phase of the treatment, but it is a very rewarding phase. I insist on this point so that we shall not expose ourselves to failures all the more bitter when the operation at the outset promised to yield a brilliant result. And I recall what Heitz has recently written :[8] it is the mixed method (operation on the sympathetic followed by the treatment indicated above) which has given in the service of M. Babinski the best results.

For the paralyses connected with vascular obliterations, associated or not with nerve lesions, sympathectomies have improved the condition without giving, except in one case, a true functional result. In such case the sympathectomy should be done to modify the vascularization of the paralyzed segment, to check the fibrous regression of the muscles. It cannot constitute of itself a sufficient treatment, but it has appeared to me to be interesting and useful. The future will determine its indication.

It is the same in regard to the value of sympathectomy associated with operations upon the nerves in cases of rebellious contracture of the median or of the ulnar nerve variety. One cannot say definitely, but the question appears to me to merit consideration."

In order to estimate the results of sympathectomy I have striven to be as concrete as possible; I have appraised as nil any result which was without value for the patient. The verdict may perhaps appear to be very reserved. Truly, I believe that the operation is a very interesting one and a useful expedient to which one may resort in cases, very diverse, which have been irresponsive to all other treatments; but it remains for us to define clearly the indications for it.

9   Recently I tried to arrest, by sympathectomy, the appearance of gangrene after resection of the popliteal vessels. The operation was followed by complete disappearance of the pains; it changed the hue of the violet-colored spots which covered the limb   For 36 hours I hoped for a therapeutic result, but none appeared, and I had to amputate the thigh.

THE PATHOLOGY OF CHROMIDROSIS.*

M. L. HEIDINGSFELD, Ph. B., M. D.

Cincinnati.

The name chromidrosis implies an anomalous secretion from the sudoriferous or sweat glands characterized by colored perspiration. Its occurrence is exceedingly infrequent; Foot,[1] in a careful review of the lierature dating from 1709 to 1868, has been able to enumerate but 38 cases, to many of which a doubtful character must necessarily be attributed. Fowie's[2] careful historical review, 1709-1891, does not add many well-defined cases, and surprisingly few have been reported in the literature of recent years. Its marked infrequency can be best appreciated by referring to the Van Harlingen's[3] statement, that "it is so rare as to be a curiosity rather than a disease."

Those who have written on the subject, almost without exception, are of one accord as to nature, and attribute to the condition a disorder, functional or otherwise, of the sweat glands. This is especially evident in all the textbooks of skin diseases, where the subjects are not alphabetically arranged and follow some system of classification (Hyde,[4] Hardaway,[5] Morrow,[6] Kaposi,[7] Duhring,[8] Joseph,[9] Stelwagon,[10] Shoemaker,[11] Schamberg,[12] Fox,[13] Gottheil,[14] etc.); in these the affection is invariable classed with the anomalies of glandular secretion, namely, the sudoriferous glands, and is grouped with hyperidrosis, anidrosis, bromidrosis, uridrosis, hematidrosis, etc. In those which follow an alphabetic arrangement an anomaly of secretion is, as a rule, directly attributed, or indirectly implied (Jackson,[15] Van Harlingen,[16] etc.), apparently a few (Lesser,[17] Mracek,[18] Bulkely,[19] Neumann,[20] etc.), studiously refrain from committing themselves. It is surprising that some of the earliest observers (Nelligan, Wilson and Gintrac) have attributed the condition to a stearrhea, and Turenne to a metastasis of the eye pigment, facts which seem not so remarkable when we consider that the early investigators were very keen observers and relied almost exclusively on their powers of personal observation.

The color of the secretion varies with different cases, green, blue, purple, black, brown, yellow, red and intermediate shades. Black is the most common, occurring is one-half the cases reported by Foot. Cases characterized by red pigmentation are generally associated with a reddish incrustation of the adjacent (usually axillary) hairs, the bacteriologic examination of which reveals the condition to be due to a *Zooglea* (*Bacillus prodigiosus*), which grows in rose-red colonies and often gives a history of direct contagion. These cases cannot be properly classed with the so-called chromidrosis, but belong, by nature, with greater propriety to the class of so-called vegetable parasitic affections of the skin.

In my own clinical and private practice I have noted eight cases of this so-called red chromidrosis during the past two years, in most of which there was not only a reddish discoloration of the incrusted hairs, but also distinct reddish discoloration of the superimposed garments. If this class of cases is included, chromidrosis is by no means a rare affection, and it probably falls to the lot of nearly every close observer to note these cases from time to time. At present I have, among others, two patients under observation with this form of affection, an uncle and nephew, the latter of whom is a practicing physician, who has taken up his residence with his uncle during the past four years. The physician states that his infection is of five years' duration, and that his mother, with whom he then resided, is similarly affected, and has had her affection for almost the same length of time. His uncle acquired the affection almost four years ago, and more recently his daughter has also been infected. The axillæ in all the cases have been involved, and all the cases show the red discoloration to a marked extent. From these and other cases in the literature it is clearly evident that these forms of reddish discoloration are readily contagious, and owe their cause to a local infection, entering from without. Their parasitic nature is further evidenced by the fact that some of my cases of so-called red chromidrosis have readily yielded to a few applications of Wilkinson ointment.

Though nearly all who have reported cases of red chromidrosis have attributed the cause to a parasite, different authorities vary as to its true nature. A few (Labrares et Cabannes[21]) strongly deny its bacteriologic nature; Temple[22] attributes it to the ingestion of potassium iodid; Stott,[23] to torulæ, which grow in rose-bed colonies on potato culture at 38 C, and deep red at O C; Fowie[24] ascribes the cause to the *Bacillius prodigiosus*; Babesiu[25] to a form of *Zooglea*, and Hartzell[26] to a fungus bearing a resemblance to the *Micrococcus tetragenus*. This marged diversity of opinion induced me to make culture experiments on potato, gelatin, agar, etc. Potato cultures served the best, and though contaminations were very common, involving different forms of sarcina, staphylococci and bacilli, deep brick-red colonies could be isolated in most instances, whose microscopic appearance was a *Micrococcus tetragenus*. Inoculation experiments were not attempted.

Let us now digress from the so-called cases of red chromidrosis and resume with the more well-defined cases, in which, according to Foot,[27] 34 out of 38 were women, 19 out of 29 were unmarried, age varied from 5 to 57 years, average being 22 years; the face, particularly the eyelids, is most commonly involved and uterine disturbance and hysteria are frequently associated. In nearly all the cases the attack comes on suddenly without apparent cause, and persists usually for a few years in intermittent form.

The case which I wish to report occurred in H. O., a brunette, a native of Germany, aged 53, a merchant of intelligence, good social standing, who had been married for fifteen years and is the father of one child. His general health has been excellent; in 1898 he suffered with an attack of hepatic colic, which was followed by jaundice, and the following year, under severe medication, involving salivation, he passed a large

number of gallstones. In a short time he regained his customary good health, which has been uniformly good since 1900. In 1901, he noted for the first time that the linen of his right forearm became discolored. The discoloration was a yellowish-brown and permanent in character, so that it could not be removed in the process of laundering. The discoloration was rapid and extensive, so that in two days' time a new cuff or a new shirt sleeve was very perceptibly and indelibly discolored. The coat sleeve lining
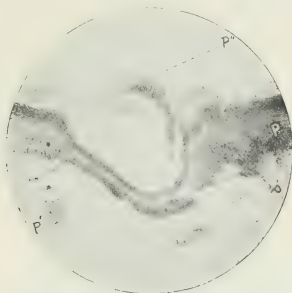
Fig. 1. Hyperkeratosis in opening of hair follicle. Accumulation of pigment in rete, P and P; in corium, P', and stratum corneum, P'', of immediate neighborhood. (Winckel, oc. 2, obj. 5.)

shared in the discoloration to such an extent that its renewal, for cosmetic reasons, every two months, became a necessity. The patient was able to take note of no other subjective or objective symptoms of any character whatever. The condition has persisted continuously for the past two years. Perspiration has not been excessive and to the patient's knowledge but slight.

When patient presented himself for examination, for the first time on March 5, 1902, the skin over the affected wrist was apparently normal; there was no evidence of any inflammation, and no disturbance of innervation. Compared with the skin elsewhere on the body and with the opposite wrist, there was a very slight, evenly-diffused
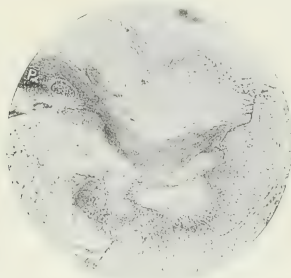
Fig. 2. Two circumscribed accumulations of pigment in rete, and corium, P and P. (Winckel, oc. 1, obj. 3.)

pigmentation, as if the affected area had been lightly bathed with tincture of opium. It remained unchanged when scrubbed with pledgets of cotton dipped in water, soap, alcohol and ether and the pledgets themselves took on no discoloration. Pledgets dipped in chloroform removed the discoloration rapidly and left the areas thus treated much whiter by contrast than the surrounding area.

Examination of urine showed reaction faintly acid, no albumin, no sugar, no formed elements, specific gravity 1020 and no indican. Blood examination by Dr. Alfred Friedlander showed no variation from the normal.

An examination of the secretion, which was collected on pure white linen, revealed it to be insoluble in the ordinary solvents, ether, alcohol, water, glycerin, xylol, etc., and readily soluble in chloroform, imparting to the latter a yellowish-brown color. Hydrogen dioxid exerts no bleaching action on the yellow color. When evaporated on glass slides it formed a smooth yellowish substance, which under the microscope revealed a semi-crystalline appearance, due no doubt to the admixture of old, dried-up epithelialcells and other detritus (Fig. 5); when previously filtered, the microscopic appearance is amorphous and structureless; when the chloroform is completely evaporated, the deposit retains a resinous character, readily taking the impression of the finger and showing with minuteness the folds and furrows of the skin, or can readily be etched by means of a needle.
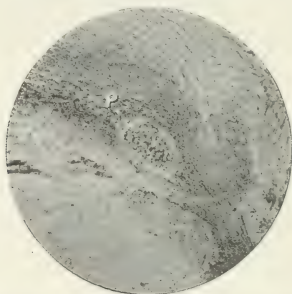
Fig. 3. Circumscribed accumulation of pigment, P, within the rete malpighi (Winckel, oc. 2, obj. 3)

The eliminated substance is unaffected by acids (nitric, hydrochloric, sulphuric, carbolic), and fails to give the characteristic reactions for indol, indican and bile pigments. The negative character of these reactions and the absence of indican in the urine is sufficient evidence, I believe, to dissociate this affection from renal and hepatic predisposing influences, notwithstanding strong opinions to the contrary (Labrares,[28] Hofmann[29]) and the pre-existing liver disorder in this particular case.

On March 8, a small piece of skin was removed from the anterior surface of the wrist, near the ulnar border, central to the area of greatest discoloration, for the purpose of microscopic examination. It was thoroughly washed for one-half hour in running water and hardened in successive alcohol; the use of formalin, Müller's fluid, etc., was purposely avoided, in order not to induce discoloration, or to conserve the blood, and thereby mask pigmentary changes. The preparation was imbedded in celloidin and sectioned in successive serials, and examined partially unstained and bleached, partially stained with polychrome-methylene-blue, eosin, hematoxylin-eosin, hematoxylin-picric acid, Van Giessen, thionin, orcein, etc. The unstained specimens and those faintly stained with polychrome-methylene-blue (Unna), decolorized with glycerin ether, showed the most interesting changes.

My interest was first centered in the microscopic appearance of the sweat glands; they are found to be normal, showing no cystic dilation, no

pigmentary infiltration, no discoloration and no inflammatory changes. In other words, no pathologic alterations, no structural variation from the normal can be detected in these elements, which, in any manner or form can induce, or result from, a so-called chromidrosis or colored sweating. (Fig. 5.) This finding accords with what would be naturally inferred from the nature of the pigmented elimination, the latter being thoroughly insoluable in water, could scarcely be eliminated by a secretion essentially watery in character.

The general appearance and structure of the skin is almost normal. The epidermis, corium and subcutaneous connective tissue are normal in their general structure and contour. The stratum corneum, rete mucosum, papillæ, capillaries, ducts of the sudoriferous glands, show no marked variations from the normal. A marked hyperkeratosis is present around the opening of the
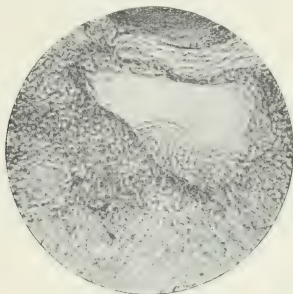
Fig. 4. Circumscribed accumulation of pigment, in corium, with a central cavernous space. (Winckel, oc. 2, obj. 5.)

hair follicles, and the adjacent stratum corneum is thickened to two or three times the natural size. (Fig. 1. Associated is the entire absence of sebaceous glands. Although hair and their follicles were abundantly present, and innumerable specimens were carefully examined, not the vestige of a sebaceous gland was discovered in any of the specimens. Elastic fibers, though abundantly present, showed no marked variation from the normal.

Examination with the higher powers of the microscope readily show the presence of small, roundish yellowish particles, which for the most part are located in definite areas of the specimens. They can be most easily detected in unstained preparations, particularly those which have been previously bleached with hydrogen dioxid, or specimens which have been very faintly stained with polychrome methylene blue, and decolorized with glycerin ether. Many are located in external layers of the stratum corneum, exclusively in and around the hair follicles, and particularly those areas

which show the above-mentioned hyperkeratosis. The greater quantity is distributed to the lower layers of the epidermis of those areas, where the pigmented bodies are accumulated to form compact masses, occasionally showing a central cavity and often distinctly walled off from the surrounding tissues. (Figs. 2, 3 and 4.) The lower layer of columnar or germinal cells of the epidermis of this region show marked pigmentation, pigment of the same form and color, as described above, and contrasting strongly with the pale germinal cells situated elsewhere along the epidermis.

In and around the papillæ, extending for some distance into the corium, and in close proximity to the hair follicles, adjacent to the pigmented germinal cells of the epidermis, are numerous small pigmented bodies, for the most part roundish, but often irregular in outline and retaining the same general analogy to the above-mentioned pigmented bodies. The latter cells
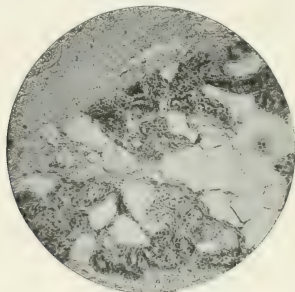
Fig. 5. Showing normal condition of the sudoriferous glands.
(Winckel, oc. 2, obj. 5.)

have an analogy to the so-called chromophore cells, which are believed to bear the pigment of normal cells from its origin in the cutis to the epidermal cells. They retain the same localization, and apparently perform the same function, the distribution of pigment from the cutis to the epidermis. They differ, however, materially in certain characteristics. They are smaller and more roundish in outline, and show no long proto-plasmic processes, so-called pseudopodia, by reason of which these cells were for a time supposed to possess ameboid movements and carry the pigment from its point of emanation to the epidermis. Ballowitz[30] has been able to demonstrate that the nerve endings penetrate these cells and envelope them thickly with dichotomous branches, thereby precluding their movement. He had also been able to demonstrate in the scales of fresh herring that the apparent change of form is due to the transportation of the pigment (which in the chromophores is finely granular) within the cells. The chromophores there-

fore probably serve as mere "stepping stones" or fixed carriers for the pigment in its course from the deeper structures to the surface. The pigmented bodies in chromidrosis differ from the chromophores of ordinary pigmentation, in that their contents are not finely granular, but homogeneous and amorphous, and that they do not decolorize with hydrogen dioxid.

I was unable to determine to my personal satisfaction the ultimate source of the pigment in chromidrosis. That its source is from some point in the cutis is readily apparent from the examination of the specimens, but whether it springs from lymph or blood vessels, from pre-existing cell tissue, or what not, will be equally if not more difficult to determine, I believe, than the present unknown source of the pigment of the cutis. Its apparently free dissemination in the epidermis, tissue preeminently vascularized
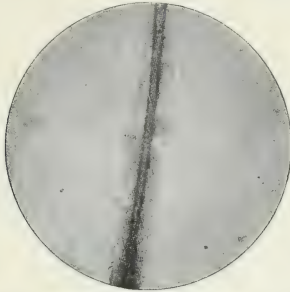
Fig. 6. Concretion attached to a hair, from a case of red chromidrosis.
(Oc. 1, obj. 3, Winckel.)

by lymph, leads me to concur with Moritz Cohn,[31] that the pigment is derived from the lymph spaces of the cutis.

I regret that I have been unable to discover in my investigations into the literature any report on the histologic changes in any of the cases thus far recorded, inasmuch as a comparison would have been of great interest and confirmation of great value. No mention of chromidrosis is made in Unna's[32] "Histopathologie der Haut," a work that is very comprehensive as regards the pathology of the skin and replete in all its detail. One case is hardly sufficient, especially in a disease which shows so many variations, to serve as a standard for all, but its marked infrequency precludes the reports of accumulated cases.

With the hope that a spectroscopic examination may have been able to shed more light on the nature of the eliminated pigment, a chloroform solution was sent to Mr. C. P. Fennel, who has kindly reported that absorption

bands were not present, and hence it was not a product of hemoglobin or oxyhemoglobin. Sodium bands, somewhat expanded, were present, together with two faint, narrow interposed lines, which could not be read with any degree of satisfaction. A careful chemical analysis has not been attempted, but for reasons above stated I do not concur that it is derived from indigo or indican, bile or hemoglobin. I believe, for the present, it can be classed with due propriety with the large class of pigments of the body, the nature of a large number of which is, as yet, so little known and imperfectly understood. I am unable to attribute to my case any direct or predisposing cause. He is of a temperate, phlegmatic disposition, quiet, unobtrusive in nature and had noted the affection over a year before he became sufficiently interested to bring it to the attention of a physician. Similation has been carefully ruled out by applying a coating of zinc gelatin to the affected area, after a
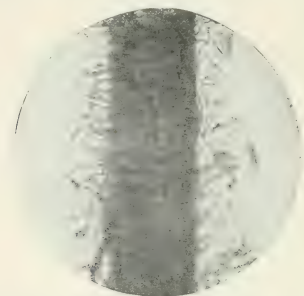
Fig. 7. Structural appearance of the concretion attached to a hair, taken from a case of red chromidrosis. (Oil immersian 1/12, oc. 4, Winckel.)

previous application of chloroform, although there were little grounds for entertaining any suspicions. He is not addicted to drugs (Temple[33]), vocation (Dyer[34]) and trauma (Geschelin[35]) exerted no predisposing influence, and he is not neurotic (Fowie,[36] Foot[37]), paretic or epileptic (Delthil[38]).

A case of simulation came to my notice in June, 1900. Miss R. F., aged 22, from Van Wert, Ohio. Consulted in regard to a reddish discoloration of the left palm and forearm, associated with shred-like desquamation of two years' duration. The case elicited much local attention and the diagnosis of erysipelas and a suggestion of amputation induced the parents to seek special advice. Red chromidrosis or simulation promptly suggested itself, and a two weeks' stay in the hospital with a plaster-of-paris bandage cleared up the condition and confirmed the latter diagnosis. A confession from the hysterical young woman then revealed that she had been in the habit of

applying crude carbolic acid locally and tinting the member with artificial rose petals dipped in water.

I have been unable to carry out any prolonged line of investigation in regard to treatment. It is somewhat difficult to suggest proper curative agents, and the same futility as regards treatment no doubt presents itself in this disease as in chloasma, vitiligo and other pigmentary disturbances. I have found that sponging the affected surface locally with chloroform is an excellent palliative measure and prevents the excessive staining so disagreeable and annoying to the patient.

To recapitulate, chromidrosis is not, as its name implies, an anomaly of sudoriferous secretion. Judging from the limited number of cases in the literature, and as a matter of common observation, it is an exceedingly rare affection as regards forms characterized by yellow and brown, and probably black, blue, green and intermediate shades of discoloration. Red chromidrosis is an entirely different and by no means an infrequent type of affection, with an extraneous cause, probably some form of erythro-micrococcus-tetragenus infection from individual to individual, and yielding to antiparasitic remedies. In the light of this investigation the pigmented elimination, in the yellowish-brown forms at least, is insoluble in water, alcohol, ether, etc., is readily soluble in chloroform, stains linen indelibly, shows no reaction when treated with ordinary reagents, and is amorphous, homogeneous and resinous in character. Pathologic examination reveals the sudoriferous glands of the affected area to be normal, sebaceous glands absent, a hyperkeratosis around the openings of hair follicles and pigment accumulations near the hair follicles, in the stratum corneum, lower layers of the rete, and the adjacent cutis. The pigment is grouped in cell-like masses, is not finely granular and does not bleach with hydrogen dioxid like chromophores. Spectroscopic examination of the eliminated pigment reveals no absorption bands and hence it is not a derivative of oxyhemoglobin. In view of the pathologic findings, the absence of sebaceous glands, the normal condition of the sudoriferous glands, cases of so-called chromidrosis (excluding red forms) are anomalies of pigmentation and not glandular secretion.

BIBLIOGRAPHY.

1. Fox, Arthur W.: Dublin Quart. Review, 1860
2. Fauve: Chromocrinie partielle et cutanée, Paris, 1864
3. Van Harlingen: Handbook of Skin Diseases, 1883, p. 29
4. Hyde: Text Book, 1900
5. Bangs and Hardaway: Text Book, 1898
6. Morrow: Text-Book, 1894
7. Kaposi: Lehrbuch, 1893
8. Duhring: Text-Book, 1877
9. Joseph: Lehrbuch, 1895
10. Stelwagon: Text-Book, 1900
11. Shoemaker: Text-Book, 1888
12. Schamberg: Text-Book, 1900
13. Fox: Atlas, 1885
14. Gottheil: Atlas and Text-Book, 1897
15. Jackson: Text-Book, 1899
16. Van Harlingen: Text-Book, 1890
17. Lesser: Lehrbuch, 1900

18. Mracek: Text-Book, 1899.
19. Bulkley: Manual of Skin Diseases, 1882.
20. Neumann: Text-Book, 1877.
21. Labrares et Cabannes: La Medicin Moderne, 58, 1896.
22. Temple, G. H.: Brit. Med. Jour., August, 1891.
23. Stott, F. W. A.: Lancet, February, 1896.
24. Fowie: Ibid.
25. Babesiu: Lancet, 1882.
26. Hartzell, M. B.: N. Y. Med. Jour., 1893
27. Foote: Ibid.
28. Labrares et Cabannes: Ibid.
29. Hofmann: Wien. Med. Woch., 1873.
30. Ballowitz, E.: Biolog. Centralblatt, 189, 19.
31. Cohn, Moritz: Monatsheft f. prak. Derm., 1891.
32. Unna: Histopathologie d. Haut, 1891.
33. Temple: Ibid.
34. Dyer, J.: Med. News, 1895.
35. Geschelin, J. S.: Jusnor Medizin, Gaz., 1894.
36. Fowie: Ibid.
37. Foote: Ibid.
38. Delthil: France Med., 1877.

BRAIN DECOMPRESSION OPERATIONS.*

By H. H. HINES, M. D.

Cincinnati

To me it does not seem justifiable at the present time, that a patient with persistent headache, vomiting not associated with the taking of food, beginning blindness, choke disc, and perhaps symptoms pointing to pressure in one of the various brain areas, should be abandoned to his unhappy fate because his physician is unable to determine the exact location and nature of the initial trouble.

It should be written in large letters that brain tumors, abscesses, cysts and infective granulomata, of the central nervous system, never were and never will be cases for medical treatment. The only hope of preventing blindness, ameliorating the other pressure symptoms or permanently curing these patients lies in early decompression, relief of pressure, and, if possible, dealing radically with the lesion.

Much valuable time has undoubtedly been lost by following the advice of numerous authorities, to subject all cases presenting symptoms of intracranial pressure to anti-syphilitic treatment. It is highly improbable that any cases of gumma *sufficiently large to produce pressure symptoms* have ever been benefited by the mercurial-iodide or the later day fad arsenical therapeusis. Gumma of the brain should be treated as any other tumor.

It is intended to include in the scope of this paper a brief discussion of cerebral, cerebellar and sellar decompression operations, first, as a purely palliative measure, and second, as a step in the radical removal of tumors, evacuation of cysts, abscesses, etc. The minute technique of these operations will not be presented, as they can be found in every modern text-book on operative surgery.

The technique of brain operations, representing the highest type of surgery, has shown marvelous progress in the past few years. The question of early and accurate localization has received much attention, and the immediate mortality, although high, is estimated at about 20 per cent. (Rawling).

However, so much depends on the nature of the growth, its position and accuracy of localization, and the personal equation (experience, skill and judgment of the operator) that it is impossible to make a definite statement as to the risk of life in brain operations. A recent writer on the subject declares that "the great secret in operating on a brain tumor lies in knowing when to terminate the attempt at removal of the tumor and when to rest content with a pure decompression" (Rawling).

There are two methods of opening the skull—(a) trephining where a button of bone is removed, the opening being subsequently enlarged by means of a rongeur forceps; and (b) craniotomy, or the trap-door method in

which a bony flap with the overlying soft parts are raised in one piece. The former procedure is the one of choice when a palliative decompression is indicated

CEREBELLAR DECOMPRESSION AND EXPLORATION.

The indications for cerebellar decompression are chiefly to relieve pressure where tumors are present in the lobes, vermis, or cerebello-pontine angle, to evacuate abscesses, remove cysts, and to drain out blood and remove clots in some cases of fracture of the posterior fossa.

PREPARATION OF THE PATIENT.

The patient is prepared as for any major operation. The entire scalp should be shaved and sterilization of the skin may be secured by either the bichloride of mercury or iodine method. The use of urotropin internally for twenty-four hours or, when feasible, for several days before operation, is recommended. This drug has been recovered from the cerebro-spinal fluid when given internally and is supposed to have antiseptic properties. Very rigid asepsis is desirable throughout the operation.

The choice of an anesthetic is worthy of some consideration. Some surgeons prefer chloroform in brain operations as it lowers the blood pressure and produces less congestion in the vessels. However, as the lowering of the blood pressure may be a source of danger and as there is some risk of paralysis of the respiratory center, oxygen may be combined with chloroform to advantage. We have used ether or the gas-oxygen-ether sequence in our operations with complete satisfaction.

The semi-reclining position in cerebral and the semi-prone in cerebellar operations is recommended.

The shock associated with brain operations is greater than with any other surgical procedure and all precautions should be taken to prevent its occurrence. The room must be warm, the table should be heated, and the patient protected by warmed blankets. Undue handling of the brain should be avoided and hemorrhage reduced to a minimum. Horsley uses a constant stream of warm saline solution which is allowed to flow over the brain during the entire time it is exposed.

Hemorrhage from the scalp may be controlled by a rubber tourniquet passed around the head, by temporary ligation of the chief vessels in the neck (Crile), or by the passage of sutures through the base of the flap (Kradel). Bleeding from the bone can be controlled by plugging with bone chips, wooden or ivory pegs, the use of Horsley's bone wax, or sterilized chewing gum (Freeman). Injured dural vessels should be ligated or encircled with fine wire clips. Bits of muscle applied to bleeding points may also be used.

For cerebellar exposures the horse-shoe shaped or cross-bow incision give the best flaps. The curved portion of the incision being carried a little

above the superior curved line of the occiput. A bone flap is seldom employed owing to the difficulty of raising the bone without injury to the adjacent sinuses; furthermore, a hernia is not apt to occur in this location because of the support of the cervical muscles after they are sutured.

Both bosses and the median ridge of the occipital bone should be removed. The amount of tension-relief obtained from a unilateral decompression is not sufficient to be of much value. The two lobes can be better compared as to tension, bulging, color, etc., and the cerebello-pontine angle can be better exposed by displacing the lobes to one or the other side in a bilateral decompression. Absence of pulsation, bulging, discoloration, increased firmness or tension on palpation are suggestive of tumor, cyst, or abscess.

Most cases are treated to best advantage by the two-stage operation—the second stage being performed from ten to twelve days later, the wound in the soft parts being entirely closed at the end of the first stage.

Defects in the dura may be remedied by transplantation of a layer of epicranium or of the fascia lata.

CEREBRAL DECOMPRESSION.

As a palliative measure and in the treatment of hemorrhage associated with fractures at the base, the sub-temporal operation of Cushing is in most favor. The principal advantage of this procedure is that hernia rarely develops, the temporal muscles and fascia giving sufficient support to prevent protrusion of the brain.

Hudson recommends W or M shaped bone sections, also trap-door bony flaps fixed in place by silver wire sutures to limit the amount of outward displacement of the flaps.

The skull may be opened at any point over the cerebrum, but if the intra-cerebral pressure is not relieved by evacuation of an abscess or cyst, or the removal of a tumor, etc., hernia of the brain is apt to occur and will prove troublesome.

The two-stage operation here, as in the cerebellum, has much to commend it

SELLAR DECOMPRESSION.

Cushing, in his recent work on diseases of the pituitary body, refers to the transnaso-sphenoidal removal of the floor of the sella turcica which has proven of value in growths and enlargements of the hypophysis. It allows of the extrusion or downward growth of the tumor mass and the consequent decrease in pressure upon the adjacent important structures. The procedure is not of value in infundibular or supra-hypophyseal conditions.

The after treatment, briefly summed up, is absolute rest and quiet in a semi-darkened room, concentrated diet (mostly fluids); the use of urotropin internally, local applications for relief of pain. Early removal of drain (if used) and strict asepsis.

In conclusion, we wish to make a plea for the early recognition and prompt surgical treatment of the cases of increased intracranial pressure. which, if taken in time, may occasionally be entirely cured or at least their headaches and vomiting may be arrested, their vision saved, often a perverted mental condition cleared up, and their last days prolonged and spent in comparative comfort. We have no doubt that there have been patients in some of our institutions for the care of mental diseases that should have had the services of a surgeon.

One of the large continental clinics makes a report of 100 brain cases that were operated upon. These are divisable into groups. There were 43 cases of suspected cerebral tumor, in 32 of which the diagnosis was correct. For cerebellar growth there were 22 operations, 11 of which confirmed the diagnosis. The remainder consisted of pontine tumors (12 cases), pituitary tumors (13 cases), decompression operations (10 cases). The proportion of incorrect to correct diagnosis in cerebral (1 in 4), and in cerebellar tumors (1 in 2) is very instructive. Of the 32 cases where a tumor of the cerebrum was found, 9 died of operation, and 12 were alive at periods varying from five years to four months.

Of 11 cases of cerebellar tumor, five died of operation, but only one patient was alive at the end of two years. Of the 12 pontine tumors only four survived the operation and these were alive for periods from two and one-half to one year afterward. (Von Eiselberg's Clinic.)

Due credit has been given for quotations from the literature.

HOSPITALS—HISTORY OF THEIR DEVELOPMENT.*

By Christian R. Holmes, M. D., F. A. C. S.

Chairman of the New Hospital Commission.

Cincinnati

The origin of hospital goes back so far into the dim past that no data is available to indicate when they were first established; but history tells us that in the eleventh century B. C. there was a college of physicians in Egypt in receipt of public pay, and regulated by law as to the nature and extent of their practice. This college belonged to the sacerdotal caste, and women were also permitted to practice medicine there. According to Pliny, as the physicians were paid officers of the State, they were required to treat the poor gratuitously. These physicians were not, however, likely to attend the sick in their own homes, or at their private consulting-rooms, except in extreme cases; and so it is presumed that, as at Athens, in Egypt, there were official houses to which the poor went at certain times, and which correspond to the out-patient departments of our hospitals, or, better still, to our dispensaries. It is further on record that Egyptian physicians, though paid by the State, were allowed to receive fees from private patients.

At Athens there were, in the fifth century B. C., physicians elected and paid by the citizens; also, according to Pindarus, dispensaries in which the physicians received their patients; and there were at least two hospitals attached to the Temple of Æsculapius. In the time of Plato some of the Athenian physicians were elected by the people and paid by the treasury. Socrates speaks of one desiring to obtain a medical appointment from the government, and there was a technical term applied especially to physicians who had a public salary. These State physicians, after election, appear to have appointed slave-doctors under them to attend the poor, while they themselves attended to the rich, and, either by their own eloquence or by that of some friendly rhetorician, persuaded the patients to drink the medicine, or submit to the knife or the hot iron. The slave-doctors, on the other hand, had no such scruples, but ran about from one patient to another, and dosed them as they thought proper, or "waited for them in their dispensaries." This passage shows that there were at Athens, in the fifth century B. C., dispensaries to which the sick poor repaired for treatment of their diseases by the slave-doctors, who were appointed and paid by the State physicians to look after ailments of the poor. These dispensaries varied in number, according to the prevalence of diseases.

In Hippocrates himself—"The Father of Medicine," as he has been called—we find the spirit which characterises our modern charity hospitals. In the oath by which he bound himself to his profession there is the declaration that he would all his life visit the sick and give them his advice gratis—

a resolution which would certainly bring him a large practice, resembling the out-patient department of a hospital; and, indeed, Pindarus tells us of houses in Athens, officially chosen, where the sick poor repaired at fixed times—in fact, dispensaries. We meet, also, with one allusion to a hospital. This institution is mentioned by the comic poet, Crates, who lived about the middle of the fourth century B. C.

That medical science had attained a high degree of perfection in Egypt may be inferred from the fact that there were specialists in different branches of the art, and each physician was allowed to practice only his own branch. The Egyptians had oculists and dentists, the latter of whom were skillful enough to be able to stop teeth with gold, as the Theban mummies show. Moreover, one of their kings—Athothis, son and successor to Menes, the first king of Egypt—wrote a treatise on anatomy. At what period medical science in Egypt emancipated itself from superstition is uncertain; but a medical papyrus, now at Berlin, which dates from the fourteenth century B. C., contains a copy of a treatise on inflammation, which, the papyrus states, was found written in "ancient writing" rolled up in a coffer, under the feet of Anubis, in the town of Sokhem, in the time of his sacred majesty, Thot the Righteous. After the death of this monarch it was handed to King Snat, on account of its importance. It was then copied and restored to its place under the feet of the statue, and sealed up by the sacred scribe and wise chief of the physicians.

In India, King Asoka, who reigned in the third century B. C., published an edict commanding the establishment of hospitals throughout his domains. Monarchs and their advisers seldom invent—they systematize; and it is more than probable that King Asoka's edict was meant to improve rather than to initiate a hospital system. The king's edicts are still extant; for they are engraven in the living rock in Gujerat, not far from the town of Surat; and there is also a legend that, grieved at seeing how often people died from diseases that could easily be cured, Asoka established dispensaries at the four gates of his royal city of Patna. The royal fashion spread, and in the year 399 A. D., six hundred years after Asoka died, a Chinese traveler, Fa-Hian, visited India, and found there hospitals, which in all essentials resembled our modern institutions. He says in his Travels: "The nobles and landowners of this country have founded hospitals in the city, to which the poor of all countries, the destitute, the cripples, the diseased, may repair for shelter. They receive every kind of requisite help gratuitously. Physicians inspect their diseases, and according to their cases, order them food and drink, decoctions or medicines, everything, in fact, that may contribute to their ease. When cured they depart at their own convenience."

Of Asoka's hospitals, one, and one only, existed at the commencement of the present century. Hospitals for the poor and sick had entirely disappeared at the time of the British occupation of India. The last remaining of Asoka's was, strange to say, devoted to the treatment of animals. It

covered twenty-five acres, and was divided into proper wards and courts for the accommodation of the patients. When an animal was sick or injured, its master had only to bring it to the hospital, where it was received and tended without regard to the caste of its owner; and, where, if necessary, it found an asylum in old age. So careful were the doctors there of the patients, that a traveler reports their purchasing bread and milk for two animals which could not crop grass.

In Rome, which so largely imitated the civilization of Greece, we find the Athenian custom of having public physicians in every city. The number of these in each center was proportionate to the number of the inhabitants, and they received salaries from the public treasury.

It should be noted, also, that the luxurious public baths erected under the Roman Empire were primarily intended for the poor. They were free to all. The subsequent abuse of them by the rich and pleasure-loving belonged to the general corruption of society which thwarted and misapplied the original charity.

The Temple of Æsculapius, situated on an island in the Tiber, was according to the practice of classic times, also a hospital and one to which certain privileges attached; for the Emperor Claudius promulgated a law which ordained that slaves whose masters abandoned them on the island of Æsculapius should be held free if they recovered from their illness.

As the Christian religion assumed importance and became paramount in the State the hospital system extended throughout the Roman Empire on lines at once more methodical and more distinctly charitable than before. Hospitals for the sick early became an integral part of society institutions. We learn that, about the year 258 A. D., Laurentius, chief of the deacons, assembled a great number of poor and sick, who were supported by the alms of the church. We cannot be sure, however, that this assemblage enjoyed medical treatment as well as alms; but it is a fact that, in the year 380 A. D., a regular hospital was founded by Fabiola, a Roman matron of distinguished piety. She instituted, St. Jerome informs us, a nosocomium, which he defines as "a house in the country for the reception of those unhappily sick and infirm persons who were before scattered among the places of public resort; where they would be furnished in a regular manner with nourishment and those medicines of which they might stand in need." This establishment was situated at some distance from the city, in a healthy part of the country. The fame of this institution spread, we are told, throughout the Roman Empire, "from the Egyptians and Parthians to the cities of Britain."

Another hospital was built by St. Basil, outside the walls of Caesarea and Cappadocia, founded, probably, on the site of an earlier hospital. This edifice was so large that St. Gregory Nazianzen says it "rose to view like a second city, the abode of charity, the treasury into which the rich poured of their wealth and the poor of their poverty. Here, disease was investigated and sympathy proved."

When St. John Chrysostom went to Constantinople, he found there at least one hospital, and built many others on the plan of the Basileas and Caesarea. There must have been a considerable number of hospitals in Alexandria about this time, for a law of the Emperor Honorius mentions no fewer than six hundred nurses, who were placed at the disposal of the bishop for the purpose of nursing the sick. Three nurses bore the name of parabolani, which originally signified nurses in infectious diseases, the title signifying those who cast themselves into danger of death with a divine recklessness.

Among the Romans, the first military hospital we hear of was established in the time of Hadrian. It was in connection with the army that hospitals which must certainly be regarded as such sprang up. In the year 90 A. D., Agathines, a Lacedemonian, opened a school of medicine in the imperial city, and about the same time institutions termed valetudinaria and veterinaria were in active operation for the treatment of infirm soldiers and their horses. They were attached to the legionary camp during war as an indispensable feature, and replaced the tent, where up till then the sick or wounded warrior had been brought. If the army changed its quarters the patient was transported to, and laid in, some neighboring cottage. Treatment appears to have been principally surgical in character. These valetudinaria were attached to the winter quarters of the soldiery, and praise was given to those generals who visited the sick and wounded. The Emperor Tiberius, both before and after his accession to the purple, was especially solicitous for his soldiers, and added to their conveniences ambulances for their easier transport, and baths for their comfort.

Military hospitals existed not only in the Eastern Hemisphere, but among the ancient Mexicans, whose strange and elaborate civilization Europeans have as yet done more to destroy than to replace. They had hospitals in their principal cities "for the cure of the sick, and for the permanent refuge of disabled soldiers." Over these hospitals were placed surgeons, who, says a grumbling chronicler—Torquemada—"were so far better than those of Europe that they did not protract the cure in order to increase the pay." (Prescott, History of the Conquest of Mexico, book 1, ch. 2.) Bancroft, in his "Native Races of the Pacific States of North America, affirms (vol. ii, p. 596 et seq.) that in all the larger Mexican cities there were hospitals amply endowed, and attended by experienced physicians, surgeons and nurses; that the Mexicans had studied and practiced medicine from ancient times; that they possessed botanic gardens, and suitable places and arrangements for dissection; that all their midwives were women; and that female doctors were common among them.

Medical women were to be found elsewhere, also, in ancient days—even in the comparatively unknown kingdom of Siam. Here still exists the oldest hospital for women of which we have any knowledge. It is in Bangkok, the capital of Siam. The inhabitants of this ancient and populous city live, for

the most part, in houses built upon rafts floating on the river Meinam; and all the physicians of the Court, both male and female, are compelled to give their services gratuitously to each of the hospitals that may require them. (Hamilton Hindostan, Vol. 1.)

From the collection of poems entitled "Shah Namah," which deals with the ancient history of Persia, we learn that the fire-worshippers had hospitals from the earliest times—an evidence of humanity which we cannot think strange in the followers of Zoroaster. The traditional stories of the tenderness of Buddha also make it natural that his followers should, as we know they have done, establish hospitals; and we read in Turnour's translation of the books of the southern Buddhists that "Buddha appointed a physician for every ten villages on the highroad, and built asylums for the crippled, the deformed, and the destitute. His son Upatisso built hospitals for cripples, for women, and for the blind and diseased; and Dhatusend built hospitals for the crippled and for the sick."

These facts indicate that hospitals, though now almost identified with the Christian religion, are the outcome of the innate tenderness that marks all noble souls, in whatever land they dwell and in whatever creed they are conceived. But, before proceeding to the consideration of the hospitals of the medieval times, it may be worth while to mention hospitals that were built for no other reason than enmity to Christ. The Emperor Julian (The Apostate) perceiving that, as he puts it, "these impious Galileans give themselves to this kind of humanity," ordered Arcacius to "establish abundance of hospitals in every city, that our kindness may be enjoyed by strangers, not only by our own people, but by those who are in need." Thus he thought to emulate and surpass the Christians.

Soon after the commencement of the Christian era, specialism prevailed to an inordinate extent, and oculists, dentists, aurists, hydropists, and even fistulists were numerous, as well as special pharmacists for herbal remedies, ointments, eye-washes, and the like. Many women practiced in those times, and lady obstetricians were in high favor. According to Haeser, open surgeries were the rule, though they varied much as to character, price and respectability. These "tabernæ medicæ" led directly to the establishment of hospitals, as it was found desirable in certain cases to have the patient under constant observation, and, so, rooms were set aside in connection with these establishments for the reception of in-patients. Galen and Plautis give particulars of the tabernae medicæ or iatria, which were erected by many towns at their own cost. They were frequently large buildings, so constructed as to admit abundance of air, and were provided with surgical instruments and medical appliances of all kinds.

Of hospitals which were not the direct off-shoots of monasteries, the oldest, so far as we can tell, is still great and flourishing—the Hotel Dieu, "God's Hostelry," in Paris, founded by St. Landry, Bishop of Paris, at his own cost in the year of 600 A. D. This was, in its original form, more than

simply a place where the sick were tended. It was a charitable organization which embraced every form of aid to the poor and needy. The functions of the inn, the workhouse, and the asylum, as well as those of the infirmary were concentrated in the Hotel Dieu.

One of the oldest English hospitals—at least the one whose reliable records bear the earliest date—is St. Bartholomew's Hospital. It was founded between 1123 and 1133 by Rahere, the jester of King Henry I. who, like the Chicot of history and the Jaques of poetry, grew tired of fooling and joined a religious order, and obtained from the king, his old master, who still cherished an affection for his faithless jester, the grant of an empty space of ground in the west suburbs of London, called Smithfield. There he built a priory, and on the south side of this he erected a hospital. The original "Bart's" though on a smaller scale than the present, was meant to fulfill a wider scope. It was meant not only for "poor diseased persons till they got well," but for reception of obstetric cases; and it also provided for the maintenance of all children in the hospital until they reached the age of seven, if their mothers had died there.

St. Bartholomew's Hospital presented from the first exceptional opportunities for the study of surgery. The original name of Smithfield was "Smoothfield," and its green meadow was a favorite scene of jousts and tournaments. A tradition of old fame, before first martyrs and then cattle became connected with it, survives in the name of "Giltspur Street," which still indicates the road by which the gaily-caparisoned knights rode to those "gentle and joyous" sports which so often ended in wounds and death. These wounded knights would, not improbably, be taken to St. Bartholomew's Hospital, where the brethren—the house-surgeons of those days—could apply oil and wine, and, where necessary, the actual cautery, or the boiling pitch, with all the skill and tenderness of which they were masters.

King John, of inglorious memory, deserves a kindly thought in connection with St. Bartholomew's Hospital for a charter confirming the annexation of the hospital to the priory, and threatening with confiscation of goods any one who should interfere with its vested interests. The individual who should separate the two branches arose some centuries later in the person of Henry VIII., who had no cause to fear King John's threat. That threat merely ordained that the goods of the wrong-doer should be confiscated to the king, so King Henry confiscated his own goods and the church's also to himself. This was naturally a serious matter, not only for the master, brethren and sisters of the hospital, but for the poor and the infirm whom they had tended there; and on a petition being laid before him by the mayor, aldermen and commonalty of the city of London, in 1538 His Majesty was pleased to permit the mayor to have the government of St. Bartholomew's Hospital; and, further, in the thirty-sixth year of his reign (1554) King Henry re-established the hospital on a secular

basis, for which he is revered as the second founder. He appointed as chief officers of the hospital a master, priest, and four chaplains, the first to be called the vice-master, the second the curate, the third the hospitaller, and the fourth the visitor of prisoners in Newgate, which stood within the parish of St. Bartholomew. Besides these there was appointed a matron with twelve sisters under her to attend to the sick.

What nursing was in those days may be gathered from the fact that these twelve nurses were ordered, when their daily work among their patients was done, to occupy themselves in spinning, sewing, mending of sheets and shirts, or some other virtuous exercise such as they should be appointed unto.

From what I have just quoted, you will see that the efforts to relieve sick and suffering humanity have perhaps existed as long as man himself in one form or another; that this phase of helpfulness to fellow human beings in distress has varied through thousands of years, depending upon the rise and fall of nations.

However, the fact remains that before the discovery of the bacterial origin of disease, about fifty years ago, especially as the result of the wonderful works of Louis Pasteur, hospitals, while intended as places of refuge and restoration to health of the sick, often became veritable pestholes, as was shown by Florence Nightingale in a table of statistics showing the mortality percentages in some of the principal hospitals of England during the year 1861. She says: "We have twenty-four London hospitals, affording a mortality of no less than 90.84 per cent., very nearly every bed yielding a death in the course of the year. Next, we have twelve hospitals in large provincial towns—Bristol, Birmingham, Liverpool, Manchester, etc., yielding a date rate of 83.16 per cent. And there are twenty-five county hospitals in country towns the mortality in which is no more than 39.41 per cent. Here we have at once a hospital problem demanding solution. However the great differences in the death rates may be explained, it cannot be denied that the most unhealthy hospitals are those situated within the vast circuit of the metropolis; and the next lower death rate takes place in hospitals in densely populated large manufacturing and commercial towns, and that by far the most healthy hospitals are those of the smaller country towns. But by far the most remarkable illustration of the effects produced on the sick and maimed by agglomeration is that afforded by the experience of the Hotel Dieu, at the latter end of the last century, and before its reconstruction. It will be observed that there was direct atmospheric communication through the entire suite of wards occupied by about 550 beds on a single floor. The whole hospital contained 1200 beds. But the number of beds by no means represented the number of sick, who were sometimes placed in the beds as close together as they could lie. In this way from 2000 to 5000, or even 7000 sick were sometimes in the hospital at one time.

"So late as the year 1788, *each of the beds* in the Hotel Dieu was intended to hold either two or four sick. There is an extremely curious notice of this

subject in M. Husson's given in Note C. From this it appears that in the sixteenth century, notwithstanding the use of multiple beds, holding, in 1515, from eight to twelve patients each, the number of sick so far exceeded the bed accommodation that the beds, in 1530, were occupied by relays of patients, and that forms were provided on which the sick whose turn it was to be out of bed could rest in the meantime."

Florence Nightingale anticipated in her writings sanitary problems that we are introducing to-day. I beg to quote a couple of passages: "Wherever cubic space is deficient, ventilation is bad. Cubic space and ventilation will, therefore, go hand in hand. The law holds good with regard to hospitals, barracks, and all inhabited places. If overcrowding, or its concomitant, bad ventilation, among healthy people, generates disease, it does so to a far greater extent among the sick is hospitals. In civil hospitals the amount of cubic space varies between 600 and 2000 cubic feet per bed. In some military hospitals it used to be under 300, and from 700 to 800 was considered a somewhat extravagant allowance. The old army practice of allotting only from 600 to 800 cubic feet per bed in hospitals was the cause why army hospitals proved to be so unhealthy. At Scutari, at one time, not even half the regulation space was given, and great overcrowding consequent thereupon was one element in the disastrous result which followed. Anyone in the habit of examining hospitals with different relative amounts of cubic space cannot fail to have been struck with the very different appearance of the sick, and with the different state of the ward atmosphere. Cubic space is an essential element in the question of ventilation. It is impossible, with due regard to warmth, to ventilate a ward in a brick or stone hospital without mechanical means when the space per bed is less than a certain amount. Crowded wards are, in fact, offensive, with all the windows open. Under all circumstances, however, the progress of the cases (in solidly-built hospitals) will betray any curtailment of space much below 1,500 cubic feet. The master of some large works in London lately mentioned the following fact: He was in the habit of sending those of his workmen who met with accidents to two different metropolitan hospitals. In one they recovered quickly; in the other they were frequently attacked with erysipelas, and some cases were fatal. On inquiry it appeared that in the former hospital a larger amount of space was allowed than in the latter, which is also so deficient in external ventilation and in construction, that nothing but artificial ventilation could effectively change its atmosphere.

"It is even more important to have a sufficient surface-area between the adjoining and the opposite beds. Piling space above the patient is not all that is wanted. In the lofty corridors of Scutari, I have seen two long rows of opposite beds with scarcely three feet from foot to foot. Certainly it cannot be thought too much, under any circumstances, to give each bed a territory to itself of at least eight feet wide by twelve or thirteen feet long.

"The want of fresh air may be detected in the appearance of patients sooner than any other want. No care or luxury will compensate, indeed, for its absence. Unless the air *within* the ward can be kept as fresh as it is *without*, the patients had better be away. What must then be said when, as in some town situations, the air *without* is not fresh air at all? Except in a few cases, well known to physicians, the danger of admitting fresh air directly is very much exaggerated. Patients in bed are not peculiarly inclined to catch cold (note 'catching cold' in bed follows the same law as 'catching cold' when up. If the atmosphere is foul, and the lungs and skin can not therefore relieve the system, then a draught upon the patient may give him cold. But this is the fault of the foul air, not of the fresh. In the wooden hospital huts before Sebastopol, with their pervious walls and open ridge ventilators, in which the patients sometimes said that they 'would get less snow if they were outside,' such a thing as 'catching cold' was never heard of. The patients were well covered with blankets, and were all the better for the cold air). In England, where fuel is cheap, somebody is indeed to blame, if the ward cannot be kept warm enough, and if the patients cannot have bed clothing enough, for as much air to be admitted from without as suffices to keep the ward fresh. *No* artificial ventilation will do this. Although in badly-constructed hospitals, or in countries where fuel is dear, and the winter very cold, artificial ventilation may be necessary—it never can compensate for the want of the open window. The ward is never fresh, when artificially ventilated. It will be found that, till the windows are opened, the air is close. A well-waged controversy has lately been carried on upon this very point, in Paris. Eminent authorities in England had decried the pavilion system, on the ground that the atmosphere of a certain Paris pavilion hospital was 'detestable,' not because of the pavilion architecture, but because of its artificial ventilation defying the best pavilion building to ventilate its patients. What is all that luxury of magnificent windows for but to admit fresh air? To shut up your patients tight in artificially warmed air, is to bake them in a slow oven. Open the windows, warm it with open fires, drain it properly, and it will be one of the finest hospitals in the world. Natural ventilation, or that by open windows and open fireplaces, is the only efficient means for procuring the life-spring of the sick—fresh air. The amount of fresh air required for ventilation has been hitherto very much underrated, because it has been assumed that the quantity of carbonic acid produced during respiration was the chief noxious gas to be carried off. The total amount of this gas produced by an adult in twenty-four hours is about 40,000 cubic inches, which in a barrack-room, say, containing sixteen men, would give 370 cubic feet per diem. Allowing eight hours for the night occupation of each room, when the doors and windows may be supposed to be shut, the product of carbonic acid would be 123 cubic feet, or about fifteen and one-half cubic feet per hour. This large quantity, if not speedily carried away, would undoubtedly be injurious to

health, but there are other gaseous poisons produced with the carbonic acid which have still greater power to injure. Every adult exhales by the lungs and skin forty-eight ounces, or three pints of water, in twenty-four hours. Sixteen men in a room would therefore exhale in eight hours, sixteen pints of water, and 123 cubic feet of carbonic acid, into the atmosphere of the room. With the watery vapor there is also exhaled a large quantity of organic matter, ready to enter into the putrefactive condition. This is especially the case during the hours of sleep, and as it is a vital law that all excretions are injurious to health if reintroduced into the system, it is easy to understand how the breathing of damp foul air of this kind, and the consequent re-introduction of excrementitious matter into the blood through the function of respiration, will tend to produce disease."

Whatever arguments there may have been against hospitals prior to the discovery of the germ origin of disease have now entirely vanished and the modern hospital, built according to the latest standards—fire-proof, germ-proof, located upon favorable sites, every bed so placed as to be bathed in life-giving sunlight and fresh, pure air, with modern laboratories containing the latest instruments of precision, a staff of highly trained physicians and nurses and dietitians, the hospital has come to not alone take care of the sick poor, but the wealthy as well—for no home can furnish all the advantages just enumerated. It is for these reasons that hospitals of the type just described are springing up all over this country and Europe with marvelous rapidity.

In Germany the number of hospitals increased from 3000 hospitals with 140,000 beds, in 1876, to 6300 hospitals with 370,000 beds, in 1900—an increase of 250 per cent. in twenty-five years. This great increase has caused many men and women to give special thought to the development and planning of these institutions.

The subject of hospital construction differs from every other kind of building, in that the various departments of medicine and sanitation in their broadest sense are constantly undergoing progressive changes, because of new discoveries, and, as a result, our efforts to meet and anticipate these new conditions in a modern hospital require unusual care and foresight in planning.

In many instances, when a municipality, or organization, or a wealthy philanthropist, determines to build a hospital, a board of directors or commissioners is created to carry out the project. The men placed in charge often have not the slightest knowledge of the needs of a hospital, be they laymen or physicians; for it is a fact that many of our most brilliant physicians have never given the subject of hospital construction any thought—and, as the subject of hospital construction is really a special department, their lack of knowledge is not so much to be wondered at—but I wish to call attention to this fact, because the general public take it for granted that every doctor must be an authority on anything pertaining to hospitals, and

hence are often misled by off-hand opinions given by members of the profession who are not qualified to speak.

The architect is often selected for reasons other than his knowledge of how to plan a hospital. The requirements of a hospital are so varied that no architect or commission can develop the best in hospital construction unless, in addition to an extensive study of what is good and what is to be avoided in existing hospitals, they call to their aid and freely profit by the advice of many of those whose lives are devoted to hospital work, who have in the school of experience discovered the good and the bad points about a hospital. I refer to the heads of every department in the hospital, from the superintendent down, and such of the medical profession as have an interest in and have conscientiously studied the subject. It also now and then happens that the architect is so intent upon attaining an imposing and architecturally perfect exterior that he sacrifices the interior to the detriment of the patients, for whose benefit the hospital was created.

While what I have said is true in the majority of instances, it is but just that I should qualify my remarks by stating that there are many exceptions in which those in charge have done everything in their power, and proceeded along correct lines to attain the best results. I believe that in the future an effort will be made by most of those who have charge of planning hospitals to gather information from every possible source.

I have carefully gone over your preliminary plans and must congratulate the gentlemen who have developed them. A few minor changes can easily be made by your supervising architect when the working drawings are prepared.

In closing I would, from my experience in hospital work, commend your efforts to establish an up-to-date hospital, but also to call your attention to the great responsibilities and large outlay of money that it involves, both in building and proper maintenance.

I. THE MEDICAL TREATMENT OF GRAVES' DISEASE WITH SPECIAL REFERENCE TO THE USE OF CORPUS LUTEUM EXTRACT.[1]

By Herman H. Hoppe, A. M., M. D.

Cincinnati

The corpus luteum has been the subject of much study in recent years and much light has been thrown upon its structure and origin, since Fraenkel's paper in 1903. Perhaps the most exhaustive and critical research both as to the origin, structure and physiology of this ductless gland has been published by Novak, who has studied its relation to menstrual disorders. Other investigators have shown that the corpus luteum has not only an influence on menstruation and pregnancy, but that it probably, by an internal secretion, which is poured directly into the circulation, has not only an influence on the development and the function of the mammary gland, but that it also has a marked influence on the secondary sex characters and therefore on the metabolism of the body as a whole.

Before going on to the subject of the relation between the corpus luteum and the thyroid gland, which is the subject of this paper, let us consider briefly what we know of the corpus luteum to-day.

We know that the normal corpus luteum is developed from the Graafian follicle. Whether it is of connective tissue or epithelial origin has been the subject of quite a dispute, but Novak, to whose article I refer those who are interested in this discussion, concludes, as a result of the study of a series of 137 ovaries removed by operation, and especially by a study of the very earliest stages of development, that it is epithelial in character and is derived from the epithelial cells of the membrana granulosa of the Graafian follicles. In this view he confirms the earlier studies of Meyer and the work of Sobotta, who prove without a doubt the epithelial origin of the corpus luteum in the lower animals. He says: "There is no reasonable doubt of the origin of the lutein cells from the epithelium of the membrana granulosa." There are two kinds of specific cells in the corpus luteum, namely, the lutein cells and the paralutein cells. In addition these cells are found to have a rich blood supply, the cells covering a very rich network of newly formed blood vessels.

It is therefore held to-day that the corpus luteum is a glandular organ, and that the epithelial cells, viz., the lutein and the paralutein cells, pour their secretion directly into the blood vessel upon which they are embedded.

The corpus luteum therefore is a ductless organ and it has a most important function in regulating the sexual life of woman. It does this probably by secreting a chemical agent into the blood stream. The effect of this chemical agent is a local one, namely, on the uterus, and perhaps a general one,

affecting the mammary glands and the metabolism underlying the development and the regulation of secondary sexual characteristics. In relation to the first function, viz., in relation to the uterus, Novak says: "There can be but little doubt that the corpus luteum possesses at least a dual function: (a) The causation of menstruation; (b) the preparation of the endometrium and the fixation of the ovum in the earliest stage of pregnancy." Novak suggests that the lutein cells stands in relation to the production of menstruation, and the paralutein cells to the function of ovum fixation. "I may simply state that in nineteen corpora lutea exhibiting marked development of the paralutein cells, all except a few were removed from patients who gave histories of profuse, and in a few instances of irregular menstruation. It is curious to note that many of these patients were sterile."

It seems therefore to have been demonstrated that the secretion of the corpus luteum has an all-important rôle in normal menstruation and in normal pregnancy. It would seem reasonable therefore to conclude that a functional decrease or a functional increase may cause amenorrhea or amenorrhagia.

Being one of the ductless glands, the ovary, perhaps through the corpus luteum, stands in relation to all the other ductless glands, and the ovary is the avenue through which all the other ductless glands exert their influence on the functions of the female generative organs.

That the corpus luteum also exerts an influence on the mammary glands and the metabolism underlying secondary sexual characteristics is at least possible. This is indicated by the research work of Seitz-Wintz and Fingerhut,[2] who think that they have isolated two active principles for the corpus luteum, which they say are opposite in their activity in relation to the functions of menstruation and pregnancy.

i. Luteolipoid which inhibits menstruation and when injected hypodermically diminishes the excessive flow.

ii. Lipamin, which in animal experiments stimulates the development of the sexual organs and when given hypodermically in amenorrhea brings on the menstrual flow. Similar observations on the relation between the corpus luteum and the mammary gland have been made by Hammond and Marshall, and very interesting observations on the relation between the corpus luteum and secondary sex characteristics were made by Pearl and Surface.

Can we regard the internal secretion of the corpus luteum as the specific internal secretion of the interstitial tissue of the ovary? Is there any other internal secretion of the ovary, which is separate and distinct from that of the corpus luteum? This question as yet is unanswered.

Now let us consider what the relations between the thyroid and the corpus luteum may be, and how a disturbance of this harmonious relation may result in hyperthyroidism.

2. Munch. Med. Wochenschrift, 1914, No. 30 + 31.

It is quite agreed that the regulation of metabolism is the function of the ductless glands, and that the thyroid's chief function is the regulation of the proteid metabolism. At any rate we conclude this to be the case, because in Graves' disease the proteid metabolism is greatly increased and in myxedema it is greatly diminished.

According to the physiological action, Falta divides the ductless glands into two groups, the acceleratory group and the retardative group, in so far as they produce acceleratory or retarding hormones. These groups through their hormones exert an antagonistic effect on the metabolic processes of the body. Thus, for example, the hormone of the thyroid gland is regarded as an acceleratory catabolic and dissimilatory. It quickens metabolism and increase excitability. This we see in Graves' disease, whereas the absence of this hormone, which we see in myxedema, causes an arrest of growth, which is regarded as the effect of the inhibition of metabolism. Opposed to this action is the group of glands with retardation, anabolistic or assimilatory hormones.[3] They build up and stimulate assimilation. The interstitial glands have also this function (interstitial tissue of the testicles, and the corpus luteum?).

On this theory one could explain the development of the Graves complex as being the result of the degeneration of the Graafian follicle. The Graafian follicle, according to this hypothesis, does not reach maturity, it does not burst, but it degenerates, undergoes liquefaction and disappears. The corpus luteum therefore is not formed and since the specific internal secretion of the ovary is the function of the mature and developed corpus luteum, this internal secretion is not produced and the chain of ductles glands is unbalanced.

The next point to consider is what causes the clinical manifestations of Graves' disease? It is needless to enter here into a critical consideration of all the various theories: the psychogenic, bulbar, cardiac, sympathetic and the thyroid theory.

We will consider the latter theory only, because in the light of the favorable results obtained by surgery, it seems to be the only tenable theory. This is also fortified by our present knowledge of the physiology of the thyroid and of the secretions of and interrelation of the whole chains of endocrine glands, and we believe that the thyroid theory explains more completely and satisfactorily the symptomatology of Graves' disease than any of the others. The next consideration is as to whether the thyroid merely gives out an excessive secretion, or whether the secretion is vitiated. Is there merely hyperthyroidism or dysthyroidism? Are we dealing with a perverted secretion or with an excessive secretion? The results obtained surgically would seem to indicate that the symptom-complex results from an excessive secretion.

According to Falta, poisoning and excessive function are merely synonymous terms; we do not need to assume a perverted function of the thyroid

---

3. Falta, page 22.

in Graves' disease. A normal secretion poured into the circulation in excess will poison the body. Falta calls our attention to adrenalin poisoning as a fitting example. We undoubtedly have in Graves' disease pluriglandular symptoms, but we need not assume from this the existence of pluriglandular disease, for we cannot have a marked hyperfunction of any one of the ductless glands without disturbing the functions of all or most of them. Our clinical experience and the theory on which the use of the extract of corpus luteum is based is that Graves' disease and hypothyroidism are equivalent terms.

It is a fairly well-established theory, and we have quoted Falta above to the effect that there is an antagonistic action on the metabolism of the body, between the thyroid glands and the interstitial sex glands. We would like to suggest as the basis of clinical experience—the treatment of Graves' disease—that the internal secretion of the corpus luteum has an inhibitory effect on the thyroid secretion, and that hyperthyroidism is an expression of a dysfunction of the corpus luteum in the female and of the interstitial glands of the testicle in the male. This view is also held by Claude and Gougerot, who speak of Graves' disease as being due to a hypovarie—a hypovarial disease.

The most serious theoretical objection to this theory is that we rarely see a typical Graves' symptom-complex follow the removal of the ovaries and testicles. We know however that after castration in both the male and in the female and during pregnancy, there is a marked increase in the size of the pituitary gland and this compensatory enlargement may mean a physiological compensation of function. This is borne out by an observation which I made in a very acute case of Graves' disease in a man, in whom the administration of an extract of the anterior lobe of the pituitary gland was followed by marked amelioration of the symptoms. Renon and Delille saw a Graves' disease symptom-complex disappear as the result of the simultaneous administration of pituitary and ovarian extract.

Clinically there is an abundance of proof that the sexual apparatus and the thyroid are closely associated. Graves' disease is found almost entirely among women, cases in men being rather rare. Women are affected at least six times as often as men and in my experience the proportion is still larger. Puberty is a very favorable time for its development. In the second place there is almost always a disturbance of menstruation; during the periods of exacerbation especially, we find very often amenorrhea or deficient menstruation. In women it occurs almost exclusively during the period of sexual life, being very rare before the age of puberty and very rarely developed after the menopause.

Pregnancy has a decided influence on the course of Graves' disease. Many women with Graves' disease do not conceive at all. In other cases we notice a decided improvement during pregnancy. In one of my cases the patient was comparatively well during one pregnancy, was rather bad

during a second, whereas an acute and violent relapse occurred during a period of amenorrhea, but she improved for a while under the effect of corpus luteum and then relapsed so acutely as to necessitate surgical intervention. Another patient who had a mild attack of Graves' disease at the age of sixteen, which disappeared after a short period of treatment, suddenly had a very acute relapse during her first pregnancy ten years later, which continued up to delivery, all symptoms disappearing very soon after the birth of the child. This rather paradoxical relation of pregnancy and Graves' disease may be explained by the fact that when the corpus luteum of pregnancy is normally developed there is an improvement in the symptoms of the patient and when the corpus luteum of pregnancy is functionally deficient there is an exacerbation of the symptoms. This is very readily understood when we consider the great rôle which the corpus luteum plays during the early part of pregnancy, at least. On the same grounds we can explain the exacerbations and remissions which occur in the course of the ordinary cases of Graves' disease. When the rupture of the Graafian follicle is followed by a normal corpus luteum the symptoms ameliorate and vice versa.

The interrelation of the thyroid and ovary is also shown by those mild cases of myxedema, which show a normal thyroid metabolism during the interval between the menstrual periods and an active myxedema during the period. It would seem to indicate that the corpus luteum exerted an inhibitory effect on the thyroid in these cases, and that the thyroid which was capable of performing its function fairly normally during the inter-menstrual period lost its ability to do so during the period of greatest activity of the corpus luteum.[4]

Is it not possible that the same interrelation between the thyroid and the corpus luteum is at least suggested by the symptom-complex of hyperthyroidism, obesity and sterility. At times in these cases the use of thyroid extract is followed by pregnancy. We also know that absolute cretins never come to puberty.

I was impelled to use the corpus luteum in a very acute case of Graves' disease three years ago, in which there was a slight enlargement of the thyroid, a loss of weight of over sixty pounds, and in which a prolonged rest cure and the ordinary Forchheimer treatment produced little or no improvement. The woman had been married twenty-five years, had never been pregnant and menstruation was now suspended for a year. The use of the ext. corpus luteum by mouth was followed by such rapid improvement in the general nervous symptoms and the cardio-vascular symptoms especially, in a very few days, that I decided to give the corpus luteum an extensive test. This first patient made a complete clinical recovery.

In the past two or three years I have treated about twenty cases of Graves' disease. The ordinary Forchheimer treatment was attended with only indifferent success. The combination, however, of the quinine hydro-

---

4   E. Hertoghe, Medical Record, 1914.

bromate, ext. belladonna with the ext. corpus luteum was found to be rapidly beneficial in nearly all the cases and the improvement was usually so rapid and so marked, in a few days to a week, to convince me that rest, diet, hygienic measures, all of which I had used for twenty years before, could not account for the result, but that the corpus luteum was the active therapeutic agent.

I wish to emphasize the fact that the above were all clinically cases of Graves' disease, no border-land doubtful cases of hyperthyroidism, in which the diagnosis might depend upon the bias of the observer. Twelve of these cases were of the more severe type with rapid emaciation, great nervous excitability, rapid pulse, pulsating thyroid gland, diarrheas, etc. The other eight were moderately severe cases. Of the very acute cases, one died. I saw this patient a week before her death, after her cases had been in an acute state, with marked mental symptoms for three months. She had the treatment for only a week and I saw her but once, and she was practically moribund at the time. A second patient in this group, who had an attack several years before, at first improved both in weight (she had lost thirty pounds), in her general nervous condition, and especially in the pulse rate, which dropped from 120 to 84 per minutes in the course of ten days. She continued to do well under the treatment for three months and then while taking the ext. corpus luteum had a very acute exacerbation with a pulse rate of nearly 200 and signs of great exhaustion and collapse. She was operated upon and the partial removal of the thyroid was followed by relief, but not by a cure, all of the symptoms of Graves' disease being present eight months after the operation.

One other very acute case was not benefited by the treatment according to her statement, although the clinical record of her case shows that her pulse rate at the first examination was 140 beats per minute, and a week later was 108. She discontinued treatment and when seen at my request a year later was in a very acute state of Graves' disease.

One of the exceedingly acute cases was a man, the only one treated. Bed rest improved him for a while, but later on he had a very acute relapse. Not knowing of any reliable preparation of the interstitial glands of the testicle, I placed this man on the ext. of the anterior lobe of the pituitary gland and he showed marked improvement while under this treatment. Later on he passed from under my supervision.

All of the other cases have improved under the treatment, all of them have the ordinary routine treatment and in addition to hygienic measures and partial rest I combine the extract of corpus luteum 0.12 with quinine hydrobrom. 0.12 and ext. belladonna 0.006 per dose.

Only one of these cases is really cured. But all the others are improved and very comfortable. The most notable improvement and the one most quickly noticed are the the cardio-vascular symptoms. The pulse rate drops very quickly and the disagreeable symptoms caused by the disturbance of

circulation quickly subside. Then the general nervous irritability diminishes and the patients all return to a more or less normal condition. I have found, however, that the patients often show a tendency to relapse and have remissions if they stop the ext. corpus luteum. If the above theory of the relation of the corpus luteum and the thyroid gland is correct, this is what we would expect. If Graves' disease is synonymous with hypovarie, with a dysfunction or a diminished function of the corpus luteum, we would get results just as those recorded above. The Graves' symptom-complex arises as a result of a defective or deficient secretion of the corpus luteum. If we replace the deficiency by the use of ext. of corpus luteum we relive the patient and improve her condition. We cannot, however, change the defective biological activity of the ovary and make a defective ovary produce a normal corpus luteum. And this is the experience in my cases. Nearly all of them require the extract continuously, sometimes one dose of the above combination per day will suffice. Others require two or three doses per day. In some of the cases there are periods of months when they are apparently free from all symptoms of Graves' disease and we may interpret these periods of remission as occurring during the time when the ovaries produce normal corpus luteum.

I believe that Graves' disease in this respect can be compared with myxedema and hypothyroidism; as long as we administer thyroid extract in these two conditions, the patients are fairly normal. As long as we administer corpus luteum in Graves' disease or in the periods of exacerbation, the patient is improved and can be kept in a fairly normal state.

BIBLIOGRAPHY.

L. Fraenkel   Arch. f. Gynaeck. 1903, Vol. 58, page 438
E. Novak   Jour. Am. Med. Assn., 1916, Vol. 67, page 1818
Falta-Meyer   The Ductless Glandular Diseases   P. Blakestons Son and Co.   2nd edition
Seitz-Wintz and Fingerhut   Munch. Med. Wochensch., 1914, No. 30-31
Hammonds and Marshall.   Proceed. Royal Society, London (B), 1914, page 422.
Pearl and Surface   Science, 1915, Vol. XLI, page 413
Claude and Gourcerot (Falta)   Gaz. d. hop. 1912, No. 57, 889
E. Hertoghe   Med. Record, 1914

II. THE TREATMENT OF HYPERTHYROIDISM WITH CORPUS LUTEUM: A SECOND REPORT.*

H. H. Hoppe, A. M., M. D.

Cincinnati

The treatment of Graves' disease is an ever interesting and important topic for discussion.

The fact that there is hardly a meeting of surgeons without a paper or even a symposium on the surgical treatment of Graves' disease and the widespread discussion of the papers shows that the surgeons have not solved the problem, notwithstanding the vogue which the surgery of the thyroid enjoys at present.

The numerous methods of treatment on a purely hygienic and medical basis and the published results of treatment is also a proof that the results of treatment from a purely medical standpoint are far from being satisfactory. Both the surgical and medical methods of attack are defective for the reason that both approach the problem from a symptomatic standpoint.

THE WEAKNESS OF SURGICAL AND DRUG TREATMENT.

The weakness of the surgical approach is that its aim is to remove the thyroid gland which is not the primary seat of disturbance but merely an expression of disordered function, whose causative seat is located in some other portion of the body. This accounts for the fact that, while undoubtedly many cases are benefitted by surgical intervention and many distressing symptoms are relieved, many of the patients, months and years after the operation, still show most of the classical signs of the disease, notwithstanding the removal of the thyroid gland. The operation has merely made the patient's condition more tolerable.

The purely drug treatment inclusive of the treatment for intestinal auto-intoxication is not often successful because it is purely symptomatic. Whatever results are obtained are the results of nature's own recuperative powers, assisted by rest and other hygienic measures.

The ideal treatment should be based upon an effort to find and remove the cause of hyperthyroidism.

THE CAUSE OF EXCESSIVE THYROID FUNCTION.

It is generally conceded that hyperthroidism is an expression of an unbalanced state of the chemical mechanism of the endocrine glands. The overactivity of the thyroid is never primary. It is unthinkable that, without any apparent cause, there should suddenly be present a state of excessive function of the thyroid. Hence our first approach toward a rational treatment

*Read before the Section on Nervous and Mental Diseases of the Ohio State Medical Association, during the Seventy-fourth Annual Meeting, at Toledo, June 1, 1920. From The Ohio State Medical Journal, October, 1920.

Page 193

of hyperthyroidism should be an endeavor to discover the cause; why the function of the thyroid, which previously has been normal, should now be excessive.

The second indication of treatment is to overcome and remove the effects, on the body as a whole, of the over-activity of the thyroid gland.

The results of the over-activity of the thyroid manifest themselves gradually and progressively on nearly all the organs and functions of the body. A whole train of signs and symptoms which may be looked upon as a result of the presence in the circulation of an excessive amount of thyroid secretion, gradually develops, which is an expression of disordered metabolism and hence, of parenchymatous changes of the tissues of all the organs of the body. Many of the effects of this disordered function persist even after the thyroid has been removed. These changes, primarily the result of toxic action of thyroid over-activity, persist even after all possiblity of thyroid action has been removed and hence demand special treatment, irrespective of the proximal cause. *The persistence of these symptoms is the best proof that, although they are originally caused by hyperthyroidism, the later condition is merely a secondary cause, the primary cause being some other remote organic or functional derangement of one of the other endocrine glands.* If this were not true such signs as exophthalmos, tachycardia, tremor, and excessive metabolism, should not persist years after the removal of the thyroid gland.

GENERAL CONSIDERATIONS OF TREATMENT.

We shall endeavor to place before you our experience in the treatment of hyperthyroidism extending over a period of five years and embracing about fifty cases. These embrace all degrees of hyperthyroidism from the mild to the most acute. None, however, were doubtful cases, the diagnosis in all being based upon the classical symptoms plus the presence of a distinct bruit in the thyroid gland. We believe that the good results in the treatment of these cases were due to the use of the extract of corpus luteum:

In treating this subject let us consider:

1. The function of the thyroid gland.
2. The relation of the thyroid to the other endocrine glands.
3. The histology and the function of the corpus luteum.
4. The clinical results obtained in the treatment of hyperthyroidism with the corpus luteum and the theory on which the treatment is based.

THE FUNCTION OF THE THYROID.

1. It seems to be fairly well established that the regulation of metabolism is one of the chief functions of the ductless glands and that the special function of the thyroid is the regulation of proteid metabolism. We see, therefore, an increase in basal metabolism in hyperthyroidism and a decrease in basal metabolism in hypothyroidism. Felta divides the ductless glands into

two groups according to their physiological function, the acceleratory group and the retardative group. Through their hormones these glands exert an antagonistic effect on the metabolism of the body.

The thyroid gland, through its hormones, quickens metabolism and increases excitability. We see this typically in hyperthyroidism in which an excess of hormones is produced. In myxoedema we have an arrest of growth due to an inhibition of metabolism, because of a deficiency in production of the hormones of the thyroid.

RELATION TO OTHER ENDOCRINE GLANDS.

2. Opposed to the acceleratory group of glands are those of the second group which have the opposite or retardative action. They build up and stimulate assimilation. In this group we have the interstitial glands, the testicles and the ovary.

We have, therefore, an antagonistic action between the thyroid gland and the sex glands and we will assume for the present, with an effort later on to offer proof, that the sex glands act as an inhibitory agency on the thyroid gland and that when there is an absence of the specific secrete of the interstitial, sex glands and the other ductless glands are unable to make the compensation, we will have an excessive function of the thyroid gland.

FUNCTION OF THE CORPUS LUTEUM.

3. We know that the specific hormone of the testicle is produced by the interstitial tissue. For the ovary, the proof of an interstitial secretory tissue has not been so well established. We shall try to offer proof that the specific hormone of the ovary is produced by the corpus luteum.

Fraenkel published a paper on the structure and origin of the corpus luteum, in 1903. Novack studied the relation of the corpus luteum to menstrual disorders and his research into its origin, structure and physiology is most critical and exhaustive. Other investigations have shown that the corpus luteum influences the development and function of the mammary gland and also that it affects the developments of secondary sex characters.

Let us consider somewhat in detail, what we know of the corpus luteum to-day. In a previous article we sought to establish the fact that the corpus luteum secretes the specific hormone of the ovary and is therefore a ductless gland. We know that the corpus luteum is the final stage of the development of the Graafian follicle. Novak made a careful study of one hundred and thirty-seven ovaries which had been removed during operation on the pelvic organs and he concludes that the corpus luteum is epithelial in character and that it is derived from the epithelial cells of the membrana granulosa of the Graafian follicles. Myer and Sobotta had previously come to the same conclusion as to the origin of the corpus luteum in lower animals.

The corpus luteum contains two kinds of specific cells—the lutein cells and the paralutein cells. These cells cover a very rich network of newly

formed blood vessels. It is held, therefore, that these cells, the lutein and paralutein cells, being epithelial, have a secretory function, that they pour their secretion directly into the blood vessels upon which they are imbedded and that the corpus luteum is therefore a ductless organ.

The most important function of the corpus luteum is the regulation of the sexual life of woman. The hormone of the corpus luteum acts in a two-fold way:

(a) A local action on the uterus and perhaps the placenta.

(b) A general one, *viz.*, the regulation of the metabolism underlying the development of the secondary sexual characteristics, seen especially perhaps in the mammary glands.

In regard to the first function Novak says: "There can be but little doubt that the corpus luteum has at least a dual function, (a) the causation of menstruation; (b) the preparation of the endometrium and the fixation of the ovum in the earliest stages of pregnancy." Novak goes further and states that he has observed in ovaries in which the paralutein cells were present in large numbers in the corpora lutea, the patients suffered from profuse menstruation, irregular periods and sterility. He believes that the lutein cells stand in relation to menstruation and that the paralutein cells have some relation to ovum fixation.

Seitz, Wintz and Fingerhut think that they have isolated the hormones of the corpus luteum and claim that it secretes two active principles which are opposite in their activity in relation to the functions of menstruation and pregnancy.

1. Luteolipoid which has an inhibitory influence on menstruation and when injected hypodermically diminishes the excessive flow in menorrhagia.

2. Lipanin, which in animal experiments, stimulates the development of the sexual organs and in human beings when administered hypodermically in amenorrhoea brings on the menstrual flow.

Hammond and Morhall have made observations on the relation between the corpus luteum and mammary glands and Pearl and Surface on the secondary sexual characteristics.

It seems demonstrated, therefore, that the corpus luteum has an all important influence, not only on menstruation and pregnancy, but also on the general metabolism of the body, in so far as the secondary sexual characteristics are concerned. There can be no doubt that other organs of internal secretion also have an influence on the regulation of the metabolism underlying secondary sexual characteristics and that these organs stand in relation to ovarian activity and that they are therefore in relation to the corpus luteum and that the latter organ is therefore the avenue through which the other ductless glands exert their influence on the functions of the female generative organs.

If these contentions of Novak, Meyer and Sobatta, that the corpus luteum is an epithelial gland and that according to Novak its function is to regulate

menstruation and ovum fixation, and if the observation of Seitz, Wintz, Fingerhut, Hammond, Marshall, Pearl and Surface on its relation to sex characteristics and mammary development are true, then there is at least some proof that there must be a specific secretion poured from the cells of the corpus luteum into the general circulation and that therefore, the corpus luteum is a ductless gland and secretes the specific hormone of the interstitial tissue of the ovary.

A defective development of the corpus luteum, therefore, would tend to produce a lack of balance of the endocrine system.

INTER-RELATION BETWEEN THE THYROID AND OVARY.

We know that there is often a lack of proper development of the Graafian follicle. In these cases the follicle does not reach maturity, it does not burst, but degenerates, undergoes liquifaction and disappears—the corpus luteum is not formed. If the corpus luteum is not formed the specific hormone of the ovary is lacking and the chain of ductless glands is unbalanced. What proof have we to uphold Felta's contention that there is a relation and perhaps an antagonistic relation between the thyroid and the ovary?

We have seen above that Felta places the thyroid gland in the group of those glands whose hormones accelerate the metabolism of the body by increased ovidation and increased excitability of the tissues, whereas he places the hormones secreted by the interstitial tissues of the sex organs in the antagonistic group, *viz.,* those whose function is to build up instead of breaking down, hormones whose function is anabolistic instead of katabolistic—assimilatory and retardative in function.

Our therapy is based upon the antagonistic action between thyroid and ovary or corpus luteum which we consider the specific endocrine gland of the ovary.

Clinically there is abundant proof of the interrelation of thyroid and sex life. In man the sexual function is an incident. In woman sexual function is the chief function of metabolism. We find, therefore, that disturbance of the thyroid activity in adults is found chiefly among women. Women are affected at least six times oftener than men and in my experience the proportion of women affected is still greater. In women, Graves' disease occurs almost always during the period of sexual life. It begins very often around puberty and its course, especially during acute exacerbations or in grave cases is attended with a suspension of the menstrual function. Graves' disease is rare before puberty and after the menopause.

INFLUENCE OF PREGNANCY.

Many women with Graves' disease do not become pregnant. This would seem to prove that a normal ovum and a normal Graafian follicle are not produced in these cases. We know that Graves' disease is subject to exacerbations and remissions. Pregnancy does occur and in some cases has a bene-

ficial effect on the course of the disease. In others pregnancy has a decidedly bad effect. In apparently cured cases pregnancy can bring on an acute attack. This paradoxical effect of pregnancy on Graves' disease may be explained by the fact that when the corpus luteum of pregnancy is normally developed there is an improvement in the symptoms of the patient and when the corpus luteum is functionally deficient there is an exacerbation of the symptoms. We would like to explain the fact that some patients may go through one pregnancy without any difficulty and the next may cause very alarming manifestations of hyperthyroidism, on this basis of either a normal or deficient corpus luteum of pregnancy. On the same grounds we would like to explain the exacerbations and remissions ordinarily seen in Graves' disease when untreated, viz., when the rupture of the Graafian follicle is followed by the development of a normal corpus luteum, the symptoms ameliorate and vice versa.

A further proof of the inter-relation of the corpus luteum and the thyroid is offered perhaps by mild cases of myxoedema which show a normal thyroid activity between menstrual periods and an active myxoedema during the menstrual function. This would seem to indicate that the corpus luteum exerted an inhibitory effect on the thyroid in these cases and that a thyroid gland, which was capable of performing its function fairly normally during the intermenstrual period, lost its ability to do so during the period of the greatest activity of the corpus luteum. (Hertoghe; Medical Record, 1914.)

Moreover, the same antagonistic action is seen in absolute Cretins who never arrive at the stage of puberty. In addition to these facts, our clinical experience would warrant our assertion that this inter-relation of thyroid and corpus luteum resolves itself into the fact that the specific hormones excreted by the corpus luteum exerts an inhibitory effect on the thyroid secretions and that hyperthyroidism is an expression of dysfunction of the corpus luteum in the female and perhaps, although we have not had much experience, of the interstitial glands of the testicle in the male. This view is also held by Claude and Gougerot, who call Graves' disease a hypoovarial disease

OBJECTION TO THE THEORY.

The most serious objection to this theory is that we rarely see a typical Graves' disease symptoms complex following the removal of ovaries or testicles. The vast majority of individuals, however, have a normal endocrine system. After a more or less prolonged period, when one gland is disturbed or diseased, it is possible for other glands to make the compensation. We know, for instance, that after castration in the human family as well as in animals, and during pregnancy for instance, there is marked increase in the size of the pituitary gland and that this enlargement means an increased function by means of which the endocrine balance is restored and maintained. Ovaries and testicles are removed only as a rule when they are

diseased and when their function has been perverted for a long time and nature has had ample opportunity to establish a compensation before the operation. It is only perhaps in individuals in whom this balance cannot be established for some reason, that a dysfunction of the interstitial sex glands is followed by hyperthyroidism. In two cases at least the use of the anterior lobes of the pituitary gland was followed by relief in male cases of Graves' disease, and Renon and Delille saw a Graves' disease symptom complex disappear as the result of the simultaneous administration of pituitary and ovarian extract.

It is essential to prove, if the above theory is correct, that the symptoms of Graves' disease are due to an excessive secretion based upon an excessive function of the gland rather than to a toxic secretion and that the manifestations of Graves' disease are due to increased thyroid activity.

THYROTOXICOSIS OR HYPER-ACTIVITY?

There have always been two theories on which the development of the symptoms of Graves' disease have been based, *viz.,* the *toxic theory* and *theory of excessive secretion.* The toxic theory is based upon the assumption of a perverted function of the thyroid gland. This theory is probably on the wane, the results obtained from surgery would seem to lead to this conclusion and the almost universal adoption of the terms hyperthyroidism and hypothyroidism would seem to indicate that the abnormal activities of the thyroid gland are due to either an excessive or a deficient secretion of the thyroid tissue. According to Felta we do not need to assume a perverted function of the thyroid, in Graves' disease, that poisoning and excessive secretion are synonymous terms. A normal secretion poured into the circulation in excess will poison the body. Felta calls our attention to adrenalin poisoning as a fitting example.

The symptom complex of Graves' disease, especially the serious cases, undoubtedly points to pluriglandular disturbance. But we need not assume that we have therefore a pluriglandular disease, for we cannot have a marked hyperfunction of any one of the endocrine glands without disturbing the function of most, if not of all of them. The theory on which the use of corpus luteum is based is that Graves' disease and hyperthyroidism are equivalent terms.

THE CORPUS LUTEUM TREATMENT OF HYPER-THYROIDISM.

4. I have been using the corpus luteum now for six years. I was impelled to try it at first on a very acute case of Graves' disease because of the presence of amenorrhœa which had persisted for a year. This patient had had prolonged rest and the usual medicinal remedies, but went from bad to worse. She had lost sixty pounds in weight. This patient made a complete recovery and has remained well for the past five years. Since my last report in 1918, I have treated twenty-five additional cases and have

had most of the cases reported previously under observation and have seen them from time to time. None of these fifty cases were doubtful cases. In making the clinical diagnosis of hyperthyroidism, I have established for myself the rule that, if there is no bruit in the thyroid gland, I do not make the positive diagnosis of hyperthyroidism and place the cases in a doubtful catagory. All of the above cases were diagnosed as positive cases on the above test. One of the cases reported in 1917, has died of influenza, all the others are doing well and some of them seem to have established a normal balance of the endocrine glands and do not take corpus luteum. The others are comfortable when they take corpus luteum.

I have had no cases of hyperthyroidism operated on since 1917. In the last group of twenty-five cases one man died twenty-four hours after I had seen him in consultation. The patient had had hyperthyroidism for years—was in an acute relapse at the time of the consultation and was suffering from and died of acute myocardial disease leading to cardiac dilatation. Three or four of these cases were very acute—one had lost sixty pounds and the other seventy pounds—both of these latter cases have made practically a complete physiological recovery and have taken up their former occupations. Both were women. Both had extreme cardio-vascular symptoms, exophthalmos, diarrhoea and rapid emaciation. One, the wife of a physician, has made a perfect recovery; the other has still some exophthalmos, and an enlarged thyroid, but insists that she is well and has worked in a factory for the past year. This second group contains a surgical case which had the thyroid removed, but still presented all the objective signs and subjective distress of hyperthyroidism. She has improved under the treatment. Three of the other cases are very much improved, all of them are satisfied and relieved. In the latter group of cases there is but one male and he has done well on extract of pituitary gland.

DETAILS OF TREATMENT.

The most notable and the most rapid improvement is seen on part of the cardio-vascular symptoms and general nervous manifestations. The pulse rate drops quickly, the general subjective symptoms caused by the circulatory disturbances subside, the loss of weight stops, digestion and appetite become normal, the nutrition improves and the patient takes on weight.

While I look upon the corpus luteum as the specific agent in the treatment of Graves' disease, I have not discontinued the symptomatic treatment, nor the attention to hygiene and diet. For after Graves' disease has been established, we see signs of pluriglandular disturbance. The digestive disturbances, the increased metabolism and the rapid emaciation all demand symptomatic treatment. On account of the general nervous and mental irritability, cases of Graves' disease are not very easily managed, nor are they as a rule faithful to the treatment. I give careful attention to the diet, allow very little physical exercise and prescribe much bed rest. Quinine hydro-

bromate and extract of belladonna are of great value. I usually give two grains of corpus extract, three grains of hydrobromate of quinine and one-tenth grain of the extract of belladonna after each meal. After the cases show improvement, I diminish the dose to two per day and even when the patients are apparently well, I still give one dose per day, usually at bedtime. As in my previous report, I still find that patients who take the treatment irregularly or who discontinue the treatment show a tendency to relapse and to have an exacerbation of all symptoms. We believe that the exacerbations and remissions which are ordinarily seen in Graves' disease are due to the fact that defective ovaries may occasionally produce even several months in succession normal corpus luteum, and during these periods show an improvement. We believe that in the cases which have recovered, the use of the corpus luteum has tided the patient over and assisted the patient in establishing a compensatory secretion by one of the other endocrine glands and thereby bringing about once more an endocrine balance with a permanent relief of all the symptoms.

CONCLUSION.

The theory on which the above treatment is based, therefore, is that hyperthyroidism is caused by a defective secretion of the interstitial sex glands; that the hormones of the interstitial sex glands have an inhibitory and regulatory action on the secretion of the thyroid; that when the function of these interstitial glands is deficient, there is a lack of physiological inhibition of the thyroid, with an excessive secretion and therefore, hyperthyroidism. In other words, hyperthyroidism and hypo-ovarianism are synonymous conditions.

As I have said before, the mere administration of corpus luteum alone will not relieve these cases. Even a superficial knowledge of Graves' disease would disabuse our minds of this idea. The cases require careful dietetic, hygienic and symptomatic treatment. But whereas my previous experience has been that most cases with the above symptomatic treatment combined with quinine hydrobromate and extract of belladonna showed but indifferent results, the use of corpus luteum, in conjunction with this general treatment, gave most satisfactory results.

The treatment of hyperthyroidism with corpus luteum is comparable with the treatment of myxœdema with thyroid extract. As long as we administer thyroid extract, cases of myxœdema and hyperthyroidism do very well. But the administration of thyroid extract will not make a defective thyroid resume a normal function. Nor will the administration of corpus luteum cause a deficient ovary to produce a mature Graafian follicle. But it has been my experience that, as long as we administer corpus luteum in Graves' disease or in its period of exacerbation, the patient is improved and can be kept in a fairly normal condition.

I. THE X-RAY EXAMINATION OF THE MASTOID REGION *

By Samuel Iglauer, B.S., M.D.

Cincinnati.

In many branches of medicine and surgery the Roentgen rays have become almost indispensable as an aid to diagnosis, and frequently the nature of some obscure condition is absolutely determined by the radiogram. The value of radiography has become well established in the field of rhinology, especially in the examination of the accessory cavities of the nose, so that sinusitis, or tumors of the antrum of Highmore, of the ethmoids, and the frontal sinus, can be definitely outlined. Radiography in rhinology not only lays bare pathologic conditions, but also gives valuable aid in outlining anatomic relations, so that the surgeon may proceed with greater assurance in opening these cavities when they are diseased. Thus Beck,[1] after obtaining an exact outline of the frontal sinus in the skiagram, turns down the anterior wall of the sinus and subsequently replaces it by a plastic operation. Ingalls[2] does not hesitate to drill into this cavity by the nasal route, after he has determined its anatomic position in the radiogram. To Caldwell[3] belongs the credit of having established the proper angle for the delineation of both frontal sinuses upon the same plate.

In exposing the temporal bone to radiographic examination, greater obstacles are to be met with than in examining the sinuses and bones of the face, because it is difficult to obtain a profile of one temporal bone without superimposing upon it the shadow of the other. In fact, the chief difficulty in radiography of the cranium is to establish the proper angle at which the picture is to be taken, in order to avoid the shadows of the thicker portion of the skull.

Thus Voss[4] and Winckler,[5] by taking pictures in the transverse diameter of the skull, report excellent results in outlining the mastoid region as well as determining its condition of health or disease.

Kuhne[6] and Plagemann[7] prefer taking pictures in the occipito-frontal direction, since thereby an image of both mastoid processes is obtained at one time and upon the same plate. Judging from the illustrations accompanying their article this method is open to objection, since the temporal bone is too far removed from the plate to give a sharp image, and only a portion of the mastoid process appears in the Roentgen picture.

Considering the difficulties frequently encountered in diagnosticating diseases of the mastoid process, it has for some time past seemed advisable to me to obtain radiograms of the mastoid region, and I was fortunate in having an expert radiologist, Dr. S. Lange, kind enough to undertake this work. To him I am indebted not only for his untiring efforts, but also for valuable suggestions.

The greatest obstacle to be overcome was in establishing the proper angle from which uniform results might be expected. At my suggestion the oblique profile of the temporal region was employed. Subsequently Dr. Lange suggested taking measurements of the angle of inclination of the X-ray diaphragm, so that greater precision might be had. These points will be further elucidated in describing the technic.

We have taken radiograms of the dry skull, of the cadaver and of a considerable number of patients. In all we have collected about fifty plates.

FIGURE 1.

Radiography of Mastoid Region, showing relative positions of plate, X-ray diaphragm and patient's head. Note the inclination of the X-ray diaphragm. (The radiograms may be taken to advantage with the patient lying on his side, but with the diaphragm in the same relative position as in Fig. I.

TECHNIC.

The technic is as follows:

A small piece of lead foil is plastered to the tip of the mastoid process in order to fix this point in the Roentgen picture. For the same reason a coil of wire is introduced into the auditory meatus. The auricle is then drawn forward and fastened by adhesive plaster to the cheek of the patient in order to hold it away from the mastoid region. The patient then lies on his side on the table, or sits upon a chair, with the ear to be examined in contact with the photographic plate. The diaphragm of the X-ray tube is then adjusted immediately below the parietal eminence on the opposite side of the patient's head, and is given a slant, so that the rays will be directed through the cranium toward the sigmoid sinus and mastoid process of the ear which is being radiographed. (See Figs. 1 and 3.) In this position, the temporal bone on the upper side of the skull is left almost entirely out of the radiographic field. Dr. Lange has measured the angle of inclination of the axis of the diaphragm and finds it to be as follows:
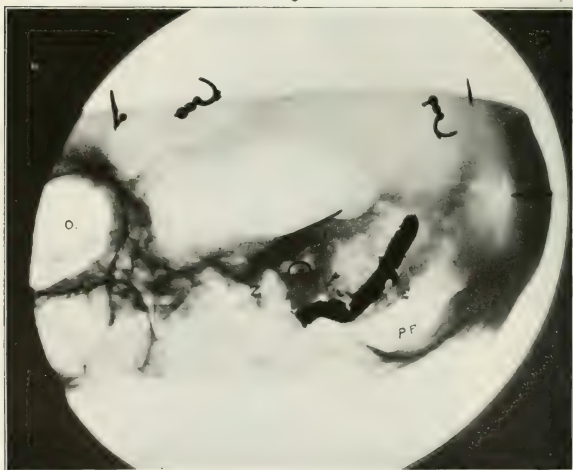
FIGURE II.

Quarter section of a skull with lead foil in the sinus, and a wire in the auditory meatus and in the middle fossa. (P F) Posterior fossa. (E) Foramen for emissary vein. (Arrow) Indicates descending portion of facial canal. (O) Orbit. (Z) Zygoma.

First, it is inclined 25 degrees to the basal plane of the skull, and secondly, it is tilted backward 20 degrees from the coronal plane of the skull. (See Fig. 1.) This step of the technic is very important because it assures uniform results.

The time of exposure varies from 20 to 50 seconds with an electrolytic interrupter, to four minutes with a mercury turbine interrupter. For comparison it is advisable to radiograph both temporal bones at the same sitting.

Figure 2 shows a quarter section of the dry skull, in which some of the landmarks are brought out by filling them with lead foil. This experiment enables the observer to fix the anatomic relations in subsequent pictures. This radiogram shows very well the internal structure and relations of temporal bones and requires no further description.

The next illustration (Fig. 3) shows the mastoid region traced from a radiogram taken through the entire skull. The anatomic structures are here
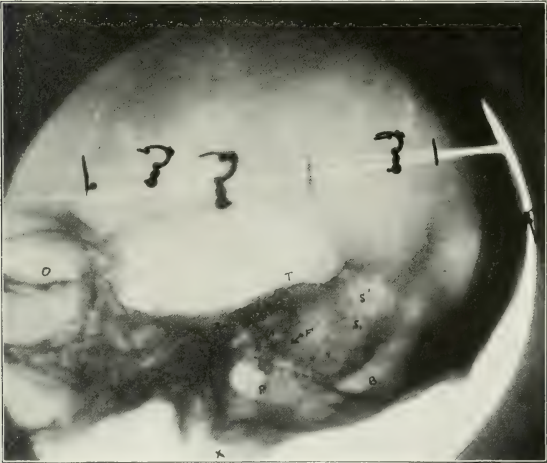
FIGURE III.

Radiogram of a dry skull, showing left mastoid region taken in an oblique profile. The lower shadow (X) is the right mastoid thrown out of the field by the oblique direction of the X-rays. (M) Meatus. (T) Tegmen. (S S) Sinus. (P) Styloid process. (Arrow) Facial canal, in the mastoid. (Z) Zygoma. (O) Orbit. (B) Floor of post-fossa.
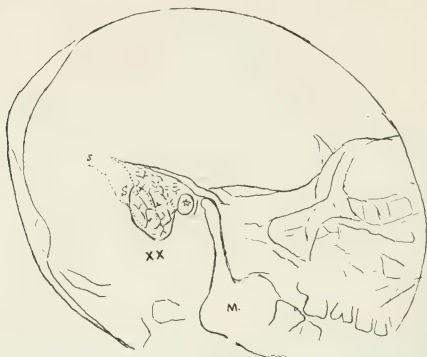
FIGURE IV.

Print and tracing from plate of a normal mastoid region in a young woman.
(*) Meatus. (X) Mastoid cells. (S S) Sinus. (M) Mandible. (E) Middle fossa.

FIGURE V.

Tracing from a radiogram of a normal, left mastoid in a man of 37. (*) Meatus.
(T) Large cell in the mastoid tip. (F) Middle fossa. (S) Sinus (?). (L L) Suture
lines. (M) Mandible. (O) Orbit.

very distinct, and it will be observed that the one mastoid is entirely out of the field.

Figures 4 and 5 are tracings from radiograms of normal mastoid regions in different patients. It is impossible to reproduce some of these plates except by tracings. These illustrations show the relative position of the middle fossa of the skull, the outline and cellular arrangement of the mastoid process, the position of the external auditory canal and frequently of the sigmoid sinus.

As may be judged from the illustrations, practically all of the skiagrams delineate very accurately the anatomic relations of the mastoid process. Considering the great variability in the structure of the temporal bone, it is apparent how valuable this knowledge obtained prior to an operation may become. Indeed, should radiography give no further information than this, it would still repay the otologist to obtain those Roentgen pictures. As a matter of fact, however, the skiagrams reveal not only anatomic relations, but also, in some cases, pathologic process in the interior of the mastoid process.

In certain cases of chronic suppurative otitis media the radiograms showed practically an absence of mastoid cells, the sclerosed bone throwing a dense shadow. Such pictures were obtained in five cases. (See Figs. 6 and 7.) In four instances the Roentgen pictures were confirmed by operation.

In one case, that of a man 21 years, with chronic otorrhea, osteosclerosis was diagnosticated in the right ear, with the probable absence of mastoid cells. (Fig. 7.) The left ear taken at the same time for comparison, showed a massively developed pneumatic process. Operation revealed a dense mastoid process with a very small antrum, which was only uncovered after working according to the method of Stacke.

A second operative case was that of a boy of twelve, with chronic suppuration in the left ear. The sinus, the tegmen tympani and the mastoid process were found exactly in the condition indicated by the picture. (Fig. 8.)

The third case was one of tuberculosis of the middle ear in a man of forty-five. The two radiograms, taken at intervals before the operation, showed a very large mastoid process of pneumatic type with hazy outlines of its cells. Operation revealed a large mastoid process with numerous large cells, most of which were filled with a clear serous fluid. The middle ear and antrum contained granulations. (Fig. 9.)

The fourth case was operated upon too recently for description.

From the experience gained by this investigation, the following conclusions may be drawn:

First. It is quite feasible to radiograph the mastoid region.

Second. The best skiagrams are obtained by directing the rays so as to give a slightly oblique profile of the temporal region.
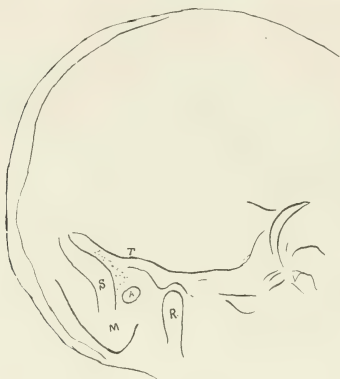
FIGURE VI.

Tracing from a radiogram. Right mastoid region in a case of chronic otorrhea of many years' standing. Note absence of mastoid cells, *i. e.*, osteosclerosis. (S) Forward-lying sinus. (M) Mastoid. (A) Meatus. (T) Tegmen. (R) Ascending ramus of mandible. (Patient of Dr. William Mithoefer.)

FIGURE VII.

(Case L.) L. K. Right mastoid region, showing: (P P) Osteosclerosis of mastoid. (S S) Sigmoid sinus. (M) Mandible. (M F) Middle fossa. (C) Meatus. (Confirmed by operation.)
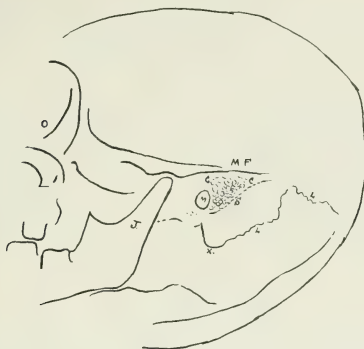
FIGURE VIII.

(Case II.) Tracing from a radiogram. Left mastoid region. (M) Meatus. (M F) Middle fossa. (C C) Mastoid cells. (S) Anterior border of sinus. (J) Mandible. (L L) Suture lines. (O) Orbit. (X) Top of mastoid.

FIGURE IX.

(Case III.) Radiogram tracing tuberculosis of middle ear and mastoid. Large mastoid of pneumatic type. Cells appear hazy in the radiogram. (Confirmed by operation.) (*) Meatus. (S) Zygoma. (O) Orbit. (M F) Middle fossa. (J) Mandible.

Third. The radiogram distinctly outlines the anatomic relations of the external auditory meatus, the limits of the mastoid process and of the mastoid cells. The floor of the middle fossa of the skull is shown, as well as the thickness of the tegmen tympani. The sigmoid sinus is frequently delineated and its position indicated.

Fourth. Osteosclerosis of the mastoid bone, following prolonged otorrhea, may in some cases be determined by the X-ray examination.

Fifth. It is possible that pus and granulations (Voss), as well as sequestra (Winckler), in the mastoid process can be diagnosticated by means of the X-ray. It must be stated, however, that acute inflammation of the mucosa is difficult to differentiate from softening of the bone (Plagemann).

Sixth. In general it may be stated that radiography should prove of great value in the determination of both the anatomic and pathologic conditions within the temporal bone.

BIBLIOGRAPHY.

1 Jos. Beck. Jour. Am. Med. Assoc., August 8, 1908

2. E. Fletcher Ingals. Jour. Amer. Med. Assoc., May 9, 1908.

3. E. W. Caldwell. Amer. Quar. of Roentgenology, January, 1907.

4. O. Vos. Verhand. der Deutsch. Otologischen Gesellschaft, May, 1907. Reprint pub. by Gustav Fischer in Jena. Also Ref. Zeitschrift f. Orenheilkunde. Bd. LIV. Heft 2, p. 208, July, 1907.

5. Winckler. Zeitschrift f. Ohrenheilkunde. Bd. LIV. Heft 2, p. 209, July 1, 1907.

6. Kuhne and Plagemann. Fortschritte auf dem Gebiete der Roentgenstrahlen. Bd. XII. Heft 5, September 1, 1908.

7. Plagemann. Verhand. der Deutsch. Roentgen-Gesellschaft. Bd. IV. September, 1908.

THE CLINICAL VALUE OF RADIOGRAPHY OF THE MASTOID REGION.*

SAMUEL IGLAUER, B.S., M.D.

Cincinnati.

The difficulties encountered in radiographing the temporal bone are due to its position at the base of the skull, to the thickness of the parts that the Roentgen rays must penetrate, and to the liability of superimposing the shadows of other portions of the skull on the skiagram. By directing the rays in the anteroposterior (posteroanterior) axis of the skull Kuhne and Plagemann[1, 2] have taken radiograms of the projecting portions of both mastoid processes, and have drawn clinical deductions therefrom. Voss[3] and Winckler[4] have obtained more detailed Roentgen pictures of the temporal bone by directing the rays in the transverse diameter of the skull.

During the past year Dr. S. Lange, radiologist to the Cincinnati Hospital, to whom I am greatly indebted, has been kind enough to undertake the radiography of the mastoid region for me. After some experimentation, at my suggestion, the radiograms were taken in an oblique profile, i. e., the rays coming from the target were made to center just below the parietal eminence on one side of the skull and were directed through the cranium in the direction of the temporal bone on the opposite side of the skull. At this angle the best skiagrams were obtained. In this position Dr. Lange found that the axis of the X-ray diaphragm was tilted upward at an agle of 25 degrees from the base of the skull (Reid's line), and that it was inclined backward 20 degrees, from the vertical plane passing through both external auditory canals. Figure 1 illustrates this double inclination. In a previous paper on this subject[5] I have given further details concerning the technic, and these need not be repeated here.

RADIOGRAPHY OF THE NORMAL MASTOID REGION.

In the normal subject; skiagrams obtained by this method delineate the following: (1) The mastoid process with its cells; (2) the position of the external auditory meatus; (3) the line marking the floor of the middle fossa; (4) frequently the position of the groove for the sigmoid sinus.

Many plates in addition show the floor of the posterior fossa, the ascending ramus of the mandible and the suture lines radiating from the asterion. Figures 2 and 3 show all the landmarks above mentioned. From

*Read in the Section on Laryngology and Otology of the American Medical Association, at the Sixtieth Annual Session, held at Atlantic City, June, 1909.

1. Kuhne and Plagemann: Fortschr. a. d. Geb. d. Roentgenstr., Sept. 1, 1908, xii, No. 1
2. Plagemann: Verhandl. d. Deutsch. Roentgen-Gesellsch., Sept., 1908, iv.
3. Vos, O.: Verhandl. d. Deutsch. Otol. Gesellsch., May, 1907; reprint pub. by Gustav Fischer in Jena; also abstr. in Ztschr. f. Ohrenh., July, 1907, liv, 208.
4. Winckler: Abstr. Ztsch. f. Ohrenh., July, 1907, liv, 209.
5 This article will appear in the Annals of Otology.
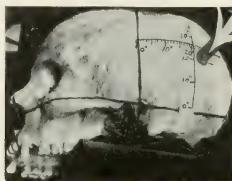
Fig. 1. The arrow indicates the inclination at which the radiogram should be taken, *i. e.*, the X-ray diaphragm should be tilted backward 20 degrees from the vertical plane, and should be inclined upward 25 degrees from the horizontal plane. (As measured by Dr. S. Lange.)

these and similar plates it will be apparent that the internal anatomy of the temporal bone may readily be determined by radiography. Considering the great variability in the structures of this bone, the knowledge so obtained prior to operation will prove of great value to the surgeon.

RADIOGRAPHY OF THE PATHOLOGIC MASTOID REGION.

Among the pathologic cases examined were seven cases of chronic otorrhea, one subacute case and four acute cases.

— In cases of suppuration of long standing, attended with osteosclerosis and obliteration of the mastoid cells, the dense bone shows very distinctly, and the sigmoid groove very often stands out sharply in the picture. The position of the antrum may be indicated if the overlying bone is not too dense.
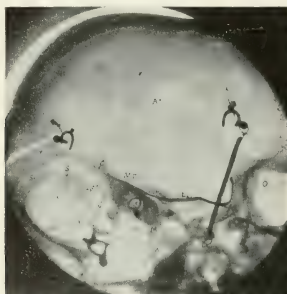
Fig. 2. Radiogram of mastoid region of a skull: (*) Auditory meatus; (M F) middle fossa; (L) lead foil in middle fossa; (C) large cell at the mastoid tip; (C') small cell; (S S) sinus (marked by wires); (B) jugular bulb; (P F) posterior fossa; (O) orbit; (X X) suture.

Seven of the cases which had been radiographed came to operation and the X-ray findings were in a great degree confirmed. It may be interesting to recount these cases somewhat in detail.

RADIOGRAMS CONTROLLED BY OPERATION.

Case 1. L. K., male, aged 21. Diagnosis: Chronic suppurative otitis media on the right (of uncertain duration). X-ray examination showed a dense shadow over the right mastoid region, with the absence of cellular structure. The position of the sinus is indicated. The left normal mastoid region showed an enormously developed pneumatic process. Operation, August 28, 1908, confirmed the findings in the right ear.

Fig. 3. Tracing from radiogram. Normal. Mastoid region of a child. (M F) Middle fossa; (C C) mastoid cells; (S S) sigmoid sinus; (J) jaw; (Z) zygoma; (P F) posterior fossa.

Remarks.—In this case it seems likely that the chronic suppuration retarded the development of the right mastoid.

Case 2. M. S., male, aged 12. Diagnosis: Chronic suppurative otitis media, right and left, of seven years' standing. X-ray examination showed a diploetic mastoid, a high tegmen, and the line marking the position of the sinus. A meatomastoid operation (November 21, 1908) showed the anatomic relations as in the radiogram.

Remarks.—The tip was not disturbed because it appeared normal in the radiogram. In the light of subsequent experience, the radiogram in this case would have indicated that operation might have been deferred.

Case 3. A. Z., male, aged 55. Diagnosis: Subacute tuberculosis of left middle ear and mastoid. X-ray examination (two plates at different times) of left ear only, showed a very large pneumatic mastoid with hazy outlines of its cells. Radical operation revealed pus and granulations in the middle ear and antrum, and showed serum in the mastoid cells, some of which extended behind the sinus.

Fig 4. Tracing from a radiogram showing osteosclerosis of mastoid (left) and a defect (?) in tegmen antri. (M) Sclerosed mastoid; (M F) middle fossa; (D) defect; (C) external auditory meatus; (J) mandible.

Fig. 5. Radiogram tracing of left mastoid region, showing osteosclerosis of mastoid process*. (M) Middle ear; (M F) middle fossa; (S S) sigmoid groove; (L L) suture lines.

Remarks.—Some of these cells might have been overlooked had they not been delineated in the radiogram.

Case 4. H. N., male, aged 62. Diagnosis: Chronic suppurative otitis media in left ear with caries of the promontory; unhealed radical mastoid in the right ear. Radiogram (Fig. 4) of left mastoid region showed dense shadow of ostersclerosis, and a few cells, just indicated, in the antrum region. A small break was noted in the line of the middle fossa and a tentative diagnosis of a defect in the tegmen antri was made. Radiogram of the right ear showed large opening made by a previous operation.

Operation.—December 29, 1908. This revealed a dense sclerosed mastoid, large antrum filled with pus and granulations, and a defect in the tegmen antri with the dura covered with granulation at this point.

Subsequent History.—The patient died on the forty-first day after the operation. Postmortem revealed tuberculous lesions in apices of both lungs and a tuberculous caries of the right internal ear and pyramid. The temporal bone, showing defect over the antrum, was removed.

Fig. 6. Tracing from a radiogram. Normal mastoid. (M) Meatus; (M F) middle fossa; (S S) sinus; (C C) posterior fossa; (P F) posterior fossa; (L L) suture lines; (J) mandible; (O) orbit; (Z) zygoma. (Right mastoid region of Case 5.)

Case 5. H. B., female, aged 4. Diagnosis: Chronic mastoiditis on the left; right ear normal. X-ray examination: An excellent picture of the left side showed a dense shadow of osteosclerosis and clear zone corresponding to the middle ear and antrum, the sinus being sharply outlined (Fig 5). The right mastoid shows normal diploetic bone and the sinus (Fig. 6). Operation January 11, 1909, showed a small fistula in the external auditory meatus leading into the antrum, which was filled with granulations; the sinus was not uncovered.

Remarks.—There is a striking contrast between the radiograms of the right and left mastoid regions.

Case 6. F. M., male, aged 2¼. Diagnosis: Acute otitis media with mastoiditis on the left. X-ray examination of the right side showed mastoid process of infantile type. The left shows the same in addition to the outlining of the posterior semicircular canal (Fig. 7). Operation January 19, 1909, revealed softened bone about the mastoid antrum.
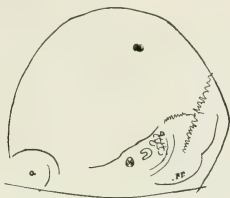
Fig. 7. Left mastoid region, showing posterior semicircular canal: (M) Meatus; (D) diploetic bone; (P F) posterior fossa; (O) orbit.

Remarks.—The outlining of the semicircular canal on the one side and not on the other would indicate that the bone over the canal was softened.

Case 7. J. R., male, aged 21. Diagnosis: Chronic suppuration in the right and left ear (of years' duration). X-ray examination (Fig. 8) of the right ear only (two pictures) showed osteosclerosis, absence of cells from the tip region and a rather forward lying sinus. The meatomastoid operation (February 3, 1909) uncovered a small deep-seated antrum with a few adjacent cells containing a few drops of pus: the sinus was not uncovered.

Remarks.—The tip of the mastoid was not disturbed, since the skiagram showed that it was not involved.

In addition to the above, five patients on whom mastoid operation had been performed were radiographed after operation, and the appearance of

Fig. 8. Tracing from radiogram: (M) Meatus; (I) antrum (?); (M F) middle fossa; (P) sclerosed mastoid process; (S) sigmoid groove; (Z) zygoma; (J) ascending ramus of upper jaw.

the operation cavity noted. One of these skiagrams taken several months after a Schwartze operation was especially interesting, since it showed that a number of cells had not been opened, and still the patient had made a perfect recovery.

The number (four) of acute cases examined is too limited to permit of any definite conclusions being drawn. One of these came to operation as already described above. The second case, that of a little girl of 10, simulated mastoiditis. The Roentgen picture of the affected side showed a haziness of the mastoid cells with clear cells on the sound side. The patient re-

covered without operation, and the radiogram taken six months after recovery showed that the cells had regained their normal contour.

The third case of acute otitis media showed similar clouding of the cells on the affected side. These two cases are interesting as confirming the contention of v. Troelsch[6] and of Politzer,[7] that the mastoid process is involved in most severe cases of acute middle-ear infection. The skiagram in the fourth case, which is too recent for complete description, shows a fistula leading into a large abscess cavity in the mastoid process. It appears probable that repeated X-ray examination in acute cases will give valuable information concerning the progress of the disease.

CONCLUSIONS.

In conclusion it may be stated:

1. The most satisfactory Roentgen pictures may be obtained in oblique profile of the temporal bone.

2. The internal anatomy of the temporal bone can be determined prior to operation, and the knowledge so obtained is a great aid to the surgeon.

3. Osteosclerosis of the mastoid secondary to chronic suppuration can usually be diagnosticated by radiography.

4. It is likely that defects in the limits of the temporal bone will appear in the radiogram.

5. Cases failing to heal after operation should be controlled by skiagraphy, as this may reveal the seat of the trouble.

6. The value of the Roentgen examination in cases of acute mastoiditis remains to be determined.

6   Troelsch, A. von: Lehrbuch der Ohrenheilkunde, Leipsic, 1881, pp. 291-410.
7   Politzer, A.: Ohrenheilkunde, 893, p. 417.

THE STRUCTURE AND MECHANICS OF DEVELOPING CONNECTIVE TISSUE.*

RAPHAEL ISAACS.

Cincinnati.

When the fluid part of blood is precipitated, the clot of fibrin has a well-developed structure of interlacing fibrils. The production of this definite structure from a fluid suggests that fibrillar appearances elsewhere in the tissues may have a similar origin. Such fibrillar textures are seen in connective tissue, in basement membranes, in cement substance between cells, and in the neurogliar tissue of the nervous system. The present paper is a study of these structures and deals with the growth, consistency, and reactions of connective tissue and cement substance. The conclusions point to the view that the so-called connective-tissue fibrils are artifacts, and that the cement substance and basement membranes are parts of a homogeneous intercellular jelly. The variation in precipitation pattern gives a histological basis for recognizing different stages in the physiology of organs.

NOMENCLATURE.

In a histological section of "fixed" connective tissue, fine fibrils can be seen stretching between the cells (Fig. 1). These are called connective-tissue fibrils (Mall, '02) or exoplasmic fibrils (Mall, '02; Flint, '04) or collaginous fibrillae (Bell '09). In the central nervous system a somewhat similar group of fibrils are known as neuroglia fibrils or fibrillated endoplasm (Hardesty, '04). The name white or collagen fibers is given to a group of highly refractive, homogeneous strands of tissue found in skin and tendon, as well as in other parts of organs. The yellow or elastic fibers are also definite large threads of tissue, found in many organs. This paper deals with the development of the white and yellow fibers, and also the intercellular jelly, a homogeneous substance lying between the cells and fibers, and giving rise, according to this view, to artificial fibrils on fixation or dehydration.

MATERIALS AND METHODS.

For the purpose of studying the structure and development of connective tissue, chick, pig, and human embryonic material of different ages was used, the fixation and staining being varied to study the effects under various conditions. Living tadpoles and embryos of the chick and pig and adult frogs were used for the study of fresh tissue. The experiments were conducted along two lines. The nature of the tissues was studied from the animal tissue, and experiments were carried out with colloid solutions of gelatin, egg albumin and fibrin, of known strength and composition, under
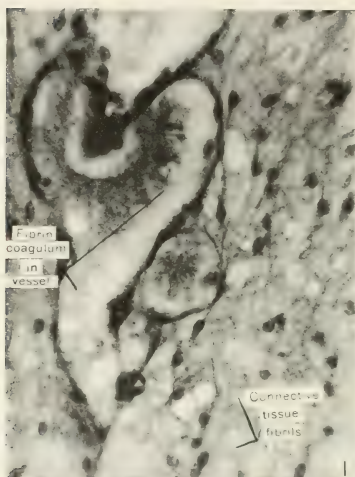
Fig. 1. Appearance of connective-tissue fibrils and fibrin clot in vessels. Photomicrograph. 55-mm. pig embryo. Bouin. Mallory's connective-tissue stain and iron haemotoxylin.

controlled laboratory conditions. The technique in each case is given under the discussion of the phenomena in question.

BEHAVIOR OF CERTAIN COLLOIDS.

In dealing with living tissues, we are studying substances in a colloid state. Some of the properties of protoplasm are properties of colloids. When we see protoplasm absorbing water or secreting it, we are naturally reminded of a similar behavior in such substances as gelatin, fibrin, or white of egg. In these substances we can, by using filtered solutions, free them from morphological structures. Yet on precipitation we can produce elaborate patterns (Hardy, '99; Butschli, '92) (Fig. 2, C). These substances, when in the jelly state, can give rise to structures, resembling fibers and fibrils, if they are put under pressure or stress. A gelatin jelly, on pressure, can be broken into many droplets of different sizes, which give rise to structures resembling fibers and other details of tissues. These structures round up into drops when pressure is released. The behavior of fresh connective tissue is much the same. When compressed between cover-glasses under
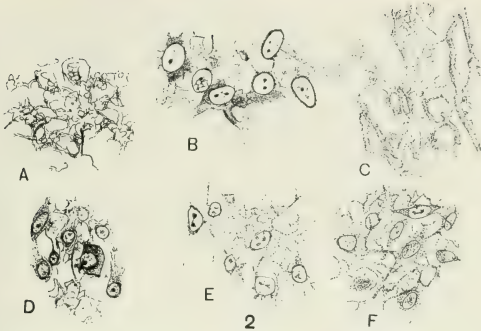
Fig. 2. Corresponding areas of subcutaneous connective-tissue of a six-day chick, fixed with various solutions and stained with Mallory's connective-tissue stain.

A. Connective tissue extract fourteen-day chick (salt solution), filtered, precipitated with Zenker's solution and stained with Mallory's connective-tissue stain. Camera-lucida drawing.

B. Fixed in Bouin's solution.

C. Egg albumin, filtered, and precipitated with Zenker's solution. Camera-lucida drawing.

D. Fixed in Zenker's solution.

E. Fixed in Van Gehuchten's solution.

F. Fixed in absolute alcohol. Camera—lucida drawings.

the microscope, we see many structures, but release of pressure results in little gelatinous droplets with but little structure.

Syneresis, the property of colloids, which give rise to the secretion of a fluid containing the substance of the colloid in a dilute state, must be taken into consideration when the colloids of the tissues are considered. This process takes place comparatively quickly when viewed under the misroscope, and a few minutes make a definite change in the consistency, toughness, and refraction of the colloid studied. The colloids which tend to undergo irreversible changes, as white of egg, show this property to a marked degree, and the differences in appearance are striking. One does not appreciate what elaborate structures and quick changes can be produced in this way until the process is studied under a high magnification. The structures produced can be emphasized by stains.

Many inorganic salts, when precipitated under the microscope, present "patterns" of interlacing fibrils, composed of strings of minute granules or cyrstals. Such pictures simulate the fibril patterns of colloidal proteins, and remind one of the delicate cytological structures often shown in fixed tissue.

THE INTERCELLULAR JELLY.

The jelly-like nature of young embryos is a matter of common experience with all who have handled young chicks or pigs. When lifted up by any part, they elongate and tend to stretch. They have the consistency of thick mucus, and a very small force is required to tear off a part or cause compression or strain. With increase of age, an increase of firmness is noted. For microscopical examination of the intercellular substance it is necessary to put small pieces in a hanging drop in a moist chamber or underneath a cover-glass on a slide, sealed with vaselin, no fluid of any kind being added. The temperature can be kept constant and evaporation can be avoided to a certain extent. However, the pulling and squeezing of the tissue in handling and cutting and the changes of tension when flattened against the cover-glass are factors to be considered in interpreting the results. Under favorable conditions, observations may be taken on the tissue for a few minutes without much physical change. Maxinow ('06, p. 683) used a somewhat similar method, but at this technique he did not show up certain cellular structures which he had expected, he emphasized these structures by producing a local oedema with physiological salt solution. The results of such a procedure, however, require cautious interpretation, as the equilibrium of the intercellular colloids is easily disturbed, a process often encountred in the physiology and pathology of connective tissue.

The subcutaneous tissue in a five-day chick reacts as a mass of jelly when touched. The tissue can be indented with a blunt needle, and the cells and substances around the point are bent. If a piece of tissue be "fixed" in this position, the position cells will show the results of the pressure, but the "connective tissue fibrils" will radiate in all directions, independently of the lines of force of the pressure. If they had been present in the living tissue, one would expect to see some results of compression, as the cells themselves show. In the living, the cells and the substance between them act as if they were a mass of the same consistency throughout, and the physiological unit for response to pulls and tension is the region affected, not separate cells.

When tissue is mounted as described, it becomes flattened against the cover-glass, and a narrow zone of a jelly-like colloidal substance, containing granules, forms the peripheral region. This jelly responds to a touch with a needle, much as does the tissue itself. On indenting one side, granules throughout the jelly move in response to the strain set up. The jelly is probably composed of intercellular substance—"tissue juice," lymph, and plasma. The intercellular colloid is more viscous than lymph, and does not run up into a capillary tube, as does the latter.

Varying with the conditions, this jelly undergoes a change on standing from two to five minutes. The granules of various kinds begin to agglutinate around the outer edge of the jelly ring, and the peripheral zone becomes stiffer. A process resembling crystallization takes place, resulting in

the formation of a network from the masses of granules. The network is microscopic, and under low power resembles a fuzzy mass with a ground-glass effect. The basis is a fine matrix of fibrillae, made up of granules, but sometimes it is fairly homogeneous. It resembles connective-tissue fibrils in appearance, taking the same stains—aniline blue, orange-G, and acid fuchsin. The behavior is similar to that of coagulating fibrin. Ranvier ('89) described a similar process as the normal method of formation of the large white fibers of the connective tissues.

This process may be hastened by drying, heat, dehydrating, and coagulating fixatives. Formalin gas produces a fairly homogeneous fixation, but dehydrating destroys this effect. The fibrils formed correspond closely to Baitsell's ('15) fibers, formed from the fibrin clot of cultures of chick tissue in vitro. He points out that "the transformation of the fibrin net results in the shrinkage of the clot. It also becomes very tough and resistant to injury." The process is hastened by mechanical manipulation of the clot with needles. This same phenomenon can be reproduced in filtered egg albumin, manipulation giving rise to the appearance of well-defined fibrils. The intercellular substance clots as if it had fibrin as its basis, but the variation in staining and the consistency during life give the impression that some mucoid elements are present in addition. The jelly is more viscid than either plasma or lymph, and does not run, as do these fluids, but it can be made to undergo a gradual flowing. This holds true for all stages, from the embryonic to the adult tissue.

As the peripheral fibrils form in our preparations, a watery fluid accumulates just around the tissue itself and in the meshes of the fibrils. This process, in effect, is analogous to that of syneresis in colloid gels, and is familiar to us in the liquid accumulation over agar-agar or gelatin jelly. It takes place independently of drying effects (Graham in M. Fischer, '15, p. 240). As soon as this dilute liquid forms, the cells in contact with it swell, probably due to the increased acid content as the tissue dies or to the availability of "free" water. This test, accompanied by the brighter appearance of the nuclei, which in the perfectly fresh tissue can be only indistinctly located, we use as signs of the beginning of the death process. The nuclei appear brighter, either because they undergo a change of consistency and become more viscous or else because the cytoplasm becomes less dense, due to the absorption of water. When the term fresh tissue is used in this paper, it refers to the condition before the appearance of these changes. The blood corpuscles do not change shape for some time after this, and appear less sensitive than the embryonic tissue cells in this respect. However, as the changes take place, the nuclei of the erythrocytes show very clearly in the chick material. The fact that blood plasma is relatively more dilute than the intercellular colloids probably accounts for this difference of behavior, and this factor should be taken into account in interpreting tissue cultures in which plasma is used. The preservation of the shape of the blood corpuscles is no test for isotonicity as far as the tissues are concerned,

as the corpuscles do not change in salt solution in the presence of "free" water (not in colloid combination). The tissue cells under these circumstances are affected immediately.

In the fresh tissue itself (chick and pig embryos) the position of the cells can be made out fairly accurately. No free-flowing intercellular "tissue lymph" can be demonstrated. On tilting a slide containing a tissue mount, the intercellular substance remains. It does not run out under pressure, showing that most of the liquid is held in colloid combination. Sufficient pressure, however, easily crushes the cells, and a considerable amount of liquid is liberated in this way. This liquid flows readily, differing from the intercellular colloid. The spaces, corresponding to the intercellular connective-tissue spaces of fixed tissue, are filled with a clear, homogeneous jelly-like substance, which, in the younger embryos, has the consistency (not necessarily concentration) of a "wobbly" gelatin gel.

The phenomenon of compression of this colloidal material is very instructive, as we can easily reproduce some of the processes taking place in the developing embryo. A needle pushed into the tissue causes a response in all parts of the tissue, as seen by the movement of visible granules. It can be described best as the jarring of a colloid jelly. Cuts close up with but little evidence of separation, and the pathway of a needle withdrawn is apparently obliterated. If a piece of the tissue is suspended from the tip of a needle or forceps, the lower end rounds up, as does a drop of stringy mucus. If a freshly cut piece of tissue is placed on top of a second piece, and the two are killed and fixed in this position, with no other pressure than the weight of the tissue, it is found on sectioning that fibrils extend in places, without interruption from piece to piece (Fig. 3). This suggests that the fibrils are formed by the dehydrating or coagulating action of the fixatives from the homogeneous jelly. If, however, the bridging fibrils were merely pre-existing fibrils of one piece which have stuck to the other piece, then we would expect the fibril to be present throughout the gap between the pieces of tissue. Fibrin would give a similar picture. The fibrils are present, however, only in places, presumably where the colloid has had time to ooze. Of course, air bubbles must be excluded. Fibrils in sections, then, may stretch across between parts which in the living may have been in contact or separated by the intercellular jelly. Sections often show such pictures around the more solid organs, as the thyroid or thymus, and they suggest that these organs evidently push into the connective tissue, which conforms to the new, irregular outline, by a flowing or oozing process, reminding one of the tissue closing in on the pathway of a withdrawn needle.

In compressed tissue, which is fixed and sectioned, the cells show the result of the pressure by their alignment—usually being flattened out, with their long axis perpendicular to the direction of the pressure—but the fibrils of the section show no evidence of the stress.

In living tadpoles Clark ('12) describes a delicate network of minute fibrillae between the cells. These, however, are not as numerous as the
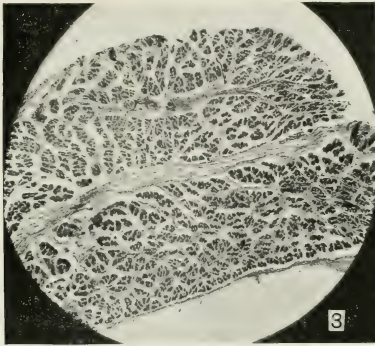
Fig. 3. Two pieces of tissue, which have been allowed to touch, and have been killed in this position. Photomicrograph. Mallory connective-tissue stain.

fibrils which the fixed tissue show. These fibrils, which are seen in the living, can be picked out from the connective-tissue fibrillae after the section is fixed, and suggest the branching cytoplasmic processes of stellate cells.

When a precipitating agent, as mercuric chloride, acts on colloidal solutions, as of egg albumin, of different strengths, the substance is precipitated in greater bulk from the more concentrated solution, and therefore leaves a denser, more closely packed mass. In the weaker solutions the mass originally is much less dense, but when it settles, the mass may appear as dense as that from the thicker solution. However, in the weaker solutions it will be noted that the supernatant solution is often cloudy, turbid, or opalescent with a fine precipitate which does not tend to settle out. In the stronger solutions, this may be carried down with the rest of the flocculent precipitate, or else in the stronger solutions, the precipitated granules are larger. A. Fischer ('99) notes that the thinner the solution of a colloid, the smaller the granules precipitated with reagents.

If, then, a weaker, but not necessarily a less viscid solution of a colloid will leave less precipitate than a more concentrated one when thrown down, then the strength of colloidal solutions in tissues can be judged by the amount of residue they leave in fixed sections. The very young embryos show a much more semi-fluid condition when picked up than the older ones. Schäfer ('12, p. 116) points out that the albuminous substances of the cell interstices of very young embryos later acquire a muco-albuminous character, and the tissue assumes a jelly-like consistency. Triepel ('11) describes

a corresponding series for fixed sections, a fine network in young stages, which becomes coarser as the embryo grows older.

On pressure on the subcutaneous connective tissues taken from a four- to seven-day chick mounted between a cover-glass and slide and sealed with vaselin, pieces can be made to separate off from the central mass, just as pieces can be broken off of a "wobbly" gelatin gel. If the microscope is tilted, these pieces will slip down, accommodating their outline to the surrounding obstacles. Such a mass, on flowing between two fixed particles (as pieces of glass), will be drawn into a very narrow thread as a string of ropy mucus. On flowing through, it is reconstituted or regathered as a mass as soon as an open space is reached (Fig. 4). The ease with which a group of cells separate and regather with little or no trace of their experience, even on fixation, suggests that the syncytial appearance of young connective-tissue cells is a temporary, apparent union of the cells, easily changed by the conditions of the environment. It is not impossible to imagine a similar process taking place on handling and fixing an embryo.
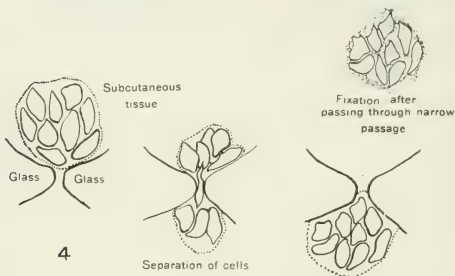
Fig. 4. Tissue from a four-day chick allowed to slip between two pieces of glass, while mounted under a cover-glass. After the entire mass squeezed through, one cell at a time, fixation shows the fibrils intact between all the cells. Camera-lucida drawings.

Lymphatic vessels and capillaries may be compressed, cell masses pushed out of their places, adhesions formed, all without leaving evidence of their original condition. This may be one way of interpreting the isolated endothelial-lined spaces and lymphatic anlagen described by Huntington ('10), McClure ('10), and Kampmeier ('12). The last points out (p. 430) that "histologically all incipient lymphatic anlagen . . . are decidedly different from either an active vein or a mature lymphatic. They lack definition and possess vague and undifferentiated outlines; for the cells of their walls are not arranged in that end-to-end fashion so characteristic of vascular endothelia. Instead, many instances were observed under strong magnification where the tissue cells in their longest diameter stand perpendicular to

the periphery of the anlagen and project far out into the lumen with their cytoplasmic filaments." Kampmeier interprets this condition as being brought about by the addition or fusion of contiguous spaces. However, these regions may have been continuous, and the apparent interruptions may have resulted from adhesions at the time of fixation.

The adhesive process may also describe the segmentation of the "retrogressive venous channels" of different authors, in which the lumen of a vessel is interrupted by solid cell masses. The value of Kampmeier's observation (p. 433) that more delicate fibrils lie in the pathway of future lymphatics is evident, as it is probable that these represent regions of less concentration than the surrounding tissue, less precipitate having been left. Kampmeier (p. 451) further observes that "the elongation of lymphatic spaces and their fusion finally into a continuous channel, as well as a growth of their cavities in diameter is accomplished by the same process which gave origin to them, namely, by the disintegration of tissue fibrils and the concentric addition of spaces." The coagulated fibrils, however, as sections show, wall off spaces in one dimension only, while in the living condition the intercellular colloid is continuous throughout the region. The correspondence of the ages of the individual embryos in which these conditions are found indicates that the intercellular substance in certain definite places is in the same physiological condition.

Inasmuch as we can conclude from Kampmeier's observations that less dense regions form in the tissue and inasmuch as we have considered the mechanism by which adhesions can be brought about, we have a physiological basis for the distribution of growing lymphatics and blood-vessels. As the free-flowing blood and lymph are confined to vessels, walled in by endothelium, the growing ends of the proliferating capillaries probably follow the lines of least resistance and therefore take the less dense pathway through the tissues. It is conceivable that regions where oxidation of acids or their neutralization becomes deficient, the tissue would absorb more water and eventually almost liquefy, allowing a growing capillary free access, and thus automatically establishing a better circulation for that part. The regions of finer fibrils in the pathway of growing capillaries strongly suggest this view. In fixed tissue it is not possible to make observations on the small changes in hydrogen ion concentrtion necessary to influence the tissues. These changes may be exceedingly small, as shown by their influence on the secreting mechanism of excised kidneys (Isaacs, '17). Furthermore, "young" capillaries of the blood and lymph system do not show concentric layers of connective tissue around them as do the larger vessels which have increased their size in situ, or more solid organs as the thyroid, thymus, or the salivary glands in the embryo, showing that little or no compression took place as the capillary grew in (Figs. 1 and 5). This holds true, even though we take into account the contraction on fixation.

THE FIBER PRODUCING CELLS.

Of cellular constituents, the spindle shape is apparently the more stable form. The multipolar forms can be considered as response forms caused by the conditions of the environment at any given moment. Ferguson ('12) and Clark ('12) have described the changes of shape of living connective-tissue cells, and their work points to the independent movement of these cells. Ferguson (p. 134) notes a change from round to stellate and stellate to round. In chick tissue, however, most of the cells take a short spindle form when surrounding tension and pressure is released. Ferguson's (p. 135) observation, that "the shape of the cell (stellate type) is undoubtedly influenced to some extent by its surroundings, and the duration of a particular stellate, spindle or lamellar shape may in some cases be thus determined," can be demonstrated by varying the pressure on the cover-glass in a tissue mount. His statement that "the general trend from round to
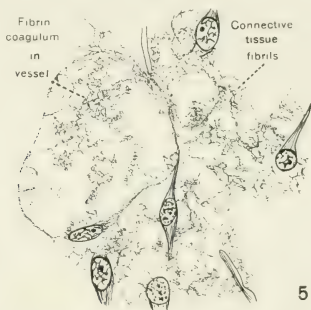
Fig. 5. Connective-tissue fibrils and fibrin in subcutaneous tissue of 55-mm. pig embryo. Fixed in Bouin. Stained in Mallory's connective-tissue stain and iron haematoxylin. Camera-lucida drawing.

stellate and from stellate to spindle is inevitable" is significant in indicating the changes of tension in the growing embryo. Rous and Jones ('16) describe a series of changes taking place in cells freed from connective tissue by digestion with 3 per cent trypsin solution. Under these conditions, the cells tend to become spherical. In our preparation we can also make the cells assume a more spherical form if any solution is added which contains more free water than the normal environment of the cells. This does take place of itself as soon as the water of syneresis forms in our preparations, as described before.

From the fact that in fresh mounts most of the multipolar or stellate cells on release from the tissue, before any stiffening takes place, assume

the spindle forms, we can assume that the factors affecting the shape of these cells are the pulls and pushes affecting the region. Change in shape of a cell thus accompanies a change in surroundings. A comparison of the more compact mesenchymal tissue (greater number of nuclei per unit area) of a 10-mm. stage with that of a 30-mm. pig shows the latter to be looser, in spite of the fact that the growing internal organs take up increased space and taking into consideration the contraction of the outer layers on fixing. Evidently the tension changes as the embryo grows. Clark ('12, p. 366) does not conclude that the change in position of individual cells can be accounted for only on a basis of general growth. When a piece of tissue is pushed with a needle under the misroscope, the mucoid nature of the mass causes it to react as a whole, each cell being affected by the surrounding push just as much as the surrounding colloid. However, the cells are in a temporary stage of unstable equilibrium, and gradually work their way in the colloid until they have reached the most stable position for the new set of conditions A demonstration of this process is seen in the descent of a piece of lead through a gelatin gel, or the conditions may be better illustrated with a watch spring embedded in gelatin of such a strength that the two bend together. After bending, the spring will eventually straighten itself by working through the gelatin. This process, which is really diapedesis, is probably the mechanism by which tissues are shaped in response to pressure or tension stimuli.

As the tissue grows older, it becomes denser, the jelly becoming thicker, and response to pulls and pushes by permanent change in form less marked, because the cells have less freedom in the thicker jelly. Kaneko ('04) describes this in granulation tissue, is which the direction of the fibers which may be formed is influenced by the direction of stresses or pulls, while this response is lost in fully formed connective tissue.

It is of course a matter of general experience that embryos shrink in fixing or during the dehydration process. While this accounts for some of the compression of layers immediately underlying the skin and around the more solid organs, some is no doubt due to the fact that organs, as the glands, in their growth, glide into the connective-tissue jelly, which is first compressed and then readjusted to the new conditions. Sections often show the connective tissue compressed, yet separated by spaces from such organs as the salivary glands or thyroid, the space being bridged here and there by fibrils. This can be interpreted as indicating that there is no firmer union between the connective tissue and the gland other than that of the general stickiness, due to the viscous intercellular substance. The relation of a gland to the surrounding connective tissue may be illustrated with gelatin solutions. A strip of a 4 per cent gelatin gel is immersed in a 2 per cent gelatin sol, and the latter allowed to gel, or it may be treated with a fixative. It will be found that the first strip, which is optically well marked off from its surroundings, retains its identity, and on being pulled out, retains some

of the weaker gelatin sticking to it. However, this can be wiped off and the two separated. This expresses the relation of a growing gland to the connective tissue.

The ease with which embryonic connective-tissue cells (four-day chick) can be separated in the fresh condition indicates that their syncytial appearance is due to adhesion. Ferguson ('12) has observed the union of cell processes in living fundulus embryos, and Clark ('12) has mapped out their successive space relations in growing tadpoles. Under such circumstances, fibrils, if present, would either anchor the cells or else leave a visible trail of the cell passage. However, in sections they surround the cells on all sides, with no appearance as the tail of a coment, that we would expect under the circumstances. On killing the tissue, contraction and great shrinkage often results in the separation of the connective-tissue cells, so that many investigators, not being able to trace the connection from one cell to another, have concluded that the cells fade out into the fibrils.

THE "FIBRILS" AND FIBER FORMATION.

That the fibrils are artificial coagulation products may be inferred from the difference in delicacy of the pattern with different fixatives (Fig. 2, B, D, E, F). Triepel ('11) notes this variation with the fixatives in studying connective-tissue fibrils and that of the coagulum in the blood-vessels in a given region in an embryo is somewhat the same. Triepel ('11) calls attention to the remarkable constancy of the pattern and its characteristic formation. This is of course natural, if the fibrillae are products precipitated by the fixatives. However, he attributes the different sizes of the fibrillar details to different amounts of shrinkage caused by different fixatives in preexistent fibrils. Hansen ('99) recognizes "pseudofibrillae" of cartilage as artifacts ("alcohol fibers" of Solger), but does not apply the principle to connective-tissue fibrils.

The fibrils take a golden-yellow color with orange-G, a light pink with acid fuchsin, and a blue with the aniline blue in Mallory's connective-tissue stain. With the latter, the bodies of the connective-tissue cells stain pink or orange-pink. (Ferguson ('11) describes the collagenous fibrils as taking a golden-brown color with Bielschowsky's silver method. From the foregoing description of the origin of the fibrils as precipitation products, we can account for the variation in results with silver-impregnation methods. The fibrils cannot be demonstrated in the fresh mount with any of the above stains nor with the so-called vital stains, until subsequent changes, possibly dehydration, lead to fibril formation.

The more solid elements of the tissue, including the white fibrous, the yellow elastic and the precartilage tissue, are formed from the intercellular jelly by the deposition of more material, making the jelly more concentrated, thus leaving more precipitate in fixed sections. The gelation and stiffening of the white and elastic fibers can be easily followed in the fresh subcu-

taneous tissue and tendons of the chick. Fresh preparations are mounted between the slide and cover, sealed, and examined immediately. Twelve-day chicks and those just hatched, illustrate the stages. While one watches through the microscope, slight pressure on the cover will serve to separate pieces of tissue. Elongated strands of tissue, stretching from piece to piece, may be seen, with occasional spindle-shaped swellings. Analysis shows that these swellings represent connective-tissue cells, adhering to a stiff, jelly-like strand of the intercellular substances. On further separation, the strand apparently elongates. The fiber is very sticky at this stage. The older stages show that the connective-tissue cells are adhering closely to a well-formed fiber, and can be dragged along the fibers when tension is put upon them. The fiber is formed of the jelly between the cells, and the increase in tough-ness from a viscid state to a well-formed fiber is shown by its changes of ex-tensibility and consistency in the fresh and the varying intensity of the
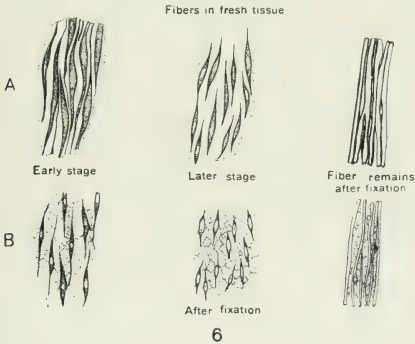
Fig. 6. Appearance of fibers in a sixteen-day chick, when flattened under a cover-glass. Successive ages are shown (A) before and (B) after fixing. Camera-lucida drawings.

staining reactions in the fixed tissue. In the early stages, a well-formed young fiber can assume the appearance of a thick network, if it is treated with a coagulating or dehydrating fluid (Fig. 6). In the latter stages the jelly becomes thick enough, so that the holes remain when cells or muscle fibers are pulled out in manipulating the tissue. The sections indicate a progressive increase in concentration due to deposition of more material, a fact shown by the increase in the amount of intercellular precipitate in sec-tions. The fibers are first laid down close together in sheets or ribbons and separate into the familiar strands only after the expansion of the surround-ing areas. Fixation, of course, separates them by shrinkage.

The speed of decolorization after staining is a factor in considering relative densities. The small fibrils lose their stain sooner than the larger, and the white fibers last of all. A. Fisher ('99) and Mann ('02), however, suggest that the greater relative surface of small particles over larger ones, in comparison to their volume, allows greater space for washing out of the stain. No fibrils can be demonstrated in the early or later stages, nor does janis green, methylene blue, or neutral red show their presence. The edema set up by the use of aqueous solutions of these salts may be temporarily avoided by dusting a few grains of the powdered stain on the tissue. The diffusion of the stain brings about the result desired from the aqueous solution by emphasizing the difference of refraction of the different constituents. As different authors have pointed out, the vital stains of this type act only on tissue which has already begun to die. Granules may dissolve some of the stain without killing the cell, however. Paramoecium, in which the posterior end is dead and consequently stained deep pink with neutral red, still retain their power of movement. Fundulus eggs can be grown in toxic solutions of substances, often, however, with the production of abnormalities. The continuation of one or more of the vital processes of a cell cannot be considered as a test of the normality, so that results with vital stains belong to the observations on experimental tissue, not necessarily normal.

The cells are probably the active agents in influencing the deposition of the material. The modern simile of an assembling and distributing plant probably describes the function of the cells in handling the materials in fiber formation. The movement and migration of the cells probably affect the distribution of the fibers and result in forming strands of the fibers, instead of one mass. The subsequent pulls and movements of the part as a whole cause the strands to glide over one another, and this is probably a second factor in the isolation of fibers. The appearance of fibers can thus be simulated in a gelatin or fibrin gel. There is some evidence to lead one to think that the cells are definitely polarized with respect to fiber-producing regions, thus accounting for the fact that some regions remain more jelly-like while neighboring regions around the same cell stiffen. The cell in profile is flattened on the fiber side, but convex on the jelly side.

Optical effects may be obtained with different concentrations of gelatin, giving the same contrast relations that are found in fresh tissues. If cubes of water-soaked gelatin of the same size are treated with dehydrating or hydrating agents of different strength (grades of alcohol, commercial formalin, Van Gehuchten's alcohol-acetic-chloroform, or corrosive sublimate), blocks of varying density are obtained. The greater the density, in this case, the greater the refractiveness (Isaacs, '16). In other words, the greater the density of a colloid of this type in the tissue, the greater its refractiveness and the lighter it appears when in focus under the misroscope. It is for this reason that the cell nuclei and fibrils as well as other elements appear clearer when the preparation is allowed to stand and undergo coagulation and dehydration changes. The change is a real one, and is not merely due.

as has often been suggested, to the eye becoming accustomed to the preparation.

The suggestion naturally follows that the fibrils may have been present as slightly more concentrated areas in the interstitial connective substance and escape detection while observed in the fresh tissue. Maxinow ('06) describes the ground substance as homogeneous, with granules which probably represent a network. Danchakoff ('08) considers that the spaces left in sections are due to extration or dissolving out of the intercellular substance. While considering the action of reagents as accounting for some granular deposits, Danchakoff describes the fibrils as cell processes. However, the precipitating action of reagents can be seen under the microscope by applying them with a delicate pipette to the undersurface of a hanging-drop preparation, thus avoiding the danger of "washing out." The action is seen to be one of condensation and precipitation of the dissolved material, leaving the fluid part in the meshes of the resulting granular coagulum. The results can be checked up with stains.

Höber ('14) states that structures produced in gelatin by alcohol are not preformed, but are produced on dehydration. In order to see if the fibrillae were performed or were artifacts, the tissue (skin, subcutaneous tissue, or muscle of a chick embryo) was pressed free from blood and lymph, and then irrigated with a potassium oxalate salt solution (Ringer's solution with potassium oxalate substituted for the calcium chloride, an empirical solution) and the solution filtered. A similar solution can be made by allowing connective tissue to stand overnight in a little Ringer's solution. Treating a drop of this solution, after filtering, with absolute alcohol or Zenker's solution on a slide, a complete network, resembling that of the tissue fibrils, was obtained, and it took the fibrillar stains (Fig. 2, A). Extracts from most tissues can be precipitated in the same way, giving fibrillar structures characteristic of each tissue. The fact that a complete network was obtained in this case would seem to indicate that the fibrillar network was an artificial precipitation product. Fixation of the washed tissue shows a decrease in the number of fibrils. The substance which was filtered evidently contained material from the more fluid intercellular substance. It is to be expected that this contained the same serum albumin, serum globulin, and fibrinogen that we normally find in the blood and lymph, and this in the end is probably the key to the network formation between the connective-tissue cells. The presence of some mucin-like substance alters the staining reaction somewhat and enables us to differentiate it from pure lymph coagulum. A similar substance and a similar network may be encountered in any tissue. The network bears the same relation to the intercellular jelly as the crystal colony bears to the solution from which it develops and is specific for each of the different colloids under the same conditions.

Fleming ('97) and others maintained that the fibers were transformations of the cel protoplasm, Meves ('10) specifying their orgin from chondrioconta at the cell surface.

FRAMEWORK OF ORGANS.

The digestion method of demonstrating fibrils, as applied by Mall ('92) and others, takes advantage of the fact that the fibrils apparently resist pancreatic digestion in alkaline solution. Mall ('02) finds that unfixed, frozen sections which are digested are difficult to stain in any satisfactory way, due to mechanical difficulties. He obtained a better picture in alcohol-fixed tissue. Flint ('04) suggests the use of alcohol-chloroform-acetic acid, sublimate acetic, or alcohol alone to show the "fibrillar framework" of organs by pancreatic digestion. Formalin cannot be used for this purpose. It will be noticed that those reagents best suited for this demonstration coagulate the homogeneous connective-tissue colloids under the microscope into the hard definite connective-tissue fibrils. Zenker's solution, while showing the fibrils, presents secondary difficulties which bar its use in digestion work. Sublimate solutions and chromium salts cannot be used advantageously in studying connective tissue, as the coagulated colloids fringe the cells with fibrils, thereby covering up many details.

Fresh tissues exposed to several changes of an alkaline solution of pancreatin for varying lengths of time (from days to weeks) without any preservative, but conducted under aseptic conditions, do not show the fibrillae when mounted under the microscope. Instead, we have a uniform jelly between the white fibers and the spaces occupied by the cells. The fibrillae, however, can be made to appear by dehydrating or coagulating agents. This enables us to interpret Mall's ('02) results when he finds that the digestion method "causes the sections, if fresh, to become a swollen and slimy mass in which the delicate fibrils can be seen after it is treated with picric acid." Picric acid precipitates the fibrils from solution. A consideration of the following test-tube experiments may be helpful in this connection. If fresh albumin is digested in an alkaline solution of pancreatin, a clear solution results. The addition of alcohol or sublimate acetic results in a flocculent precipitate (peptones). Therefore, if any product of digestion remain in the homogeneous jelly resulting from digestion, we can have just as complete a network formed as if no digestion took place. Posner and Gies ('04) point out that the "connective-tissue mucoids are readily digested by trypsin in alkaline solution." If the washing is complete enough to remove the products of digestion, then the tissue falls to pieces and the results are considered "unsatisfactory." The unreliability of digestion methods is a part of the experience of all who have used them. This would indicate the possibility that the fibrillar details in the framework of organs and basement membranes may be products of fixation. Mall ('92), Flint ('04), and Moody ('10), among others, give excellent descriptions of such digestion preparations, which, if considered from the point of view of coagulation products, indicate something of the distribution of the intercellular colloid.

NEUROGLIA AND THE INTERCELLULAR JELLY OF THE NERVOUS
SYSTEM.

The jelly-like nature of fresh nervous tissue, as the cerebral hemispheres
of the adult frog or its medulla, is a constant characteristic. This tissue
when mounted fresh between a slide and cover and sealed shows a field
of cells, nuclei, and nerve fibers imbedded in a clear homogeneous jelly. By
varying the pressure, different details can be brought out. If some alcohol
is allowed to run under the cover, the picture changes entirely. A heavy
groundwork of very delicate fibrils develop both in the tissue and in the
expressed jelly surrounding it. The nerve fibers often act as bases around
which and from which the fibrils radiate. Van Gehucten's fluid gives an
equally heavy crop of fibrils. The presence of different structures, as capil-
laries, active ciliated cells, and nerve fibers, serve often to give a clue as to
just what part of the brain wall we are studying.

Hardesty ('04) points out that the development of the neuroglia fibers
is a process of transformation of fibrillated areas. The deeply stained
fibers in the exoplasm of the syncytium of his sections are seemingly derived
from a condensation of the less deeply staining substance. However, a
study of the fresh tissue leads to the conclusion that this described for-
mation is really the result of precipitating the successive stages with the
fixative. The increase in concentration and density brought about by ad-
dition and deposition of more material to the jelly gives us a basis for varia-
tions in the pictures obtained in successive stages. Coagulation or fixation,
then, would leave a more compact mass where the fibers are, but a delicate
network ("fine threads of the spongioplasmic network" (p. 262) in the
less concentrated parts. This work corroborated Weigert's and Hardesty's
(p. 257) conclusion that "the fibers cannot be regarded in any sense as out-
growths of the cells," but, on the other hand, it indicates that we are dealing
with more or less concentrated colloids of the homogeneous intercellular
substance and that the fibrillated appearance of the so-called exoplasm is a
fixation product. Holmgren ('04) and later Ross ('15) have described
prolongations of cytoplasmic processes of glia cells, which appear in section
to run into the "trophospongia" of the nerve cells. These apparent "non-
nervous partitions of capsular processes continuous with the glia cell" are
in reality the remains of the intercellular jelly which when coagulated by the
fixative or in post-mortem processes appear to be fine protoplasmic fibrillae
continuous with the glia cells on the one hand and the trophospongia on the
other.

SUMMARY AND CONCLUSIONS

The intercellular jelly of embryonic and adult tissue is structurally
homogeneous and contains no network of fibrils. The evidence may be
summoned up as follows:

1. Fibrils cannot be seen in the living intercellular substance.
2. Fixatives, drying, dehydration, or coagulating reagents are necessary
to show the fibrillae.

3. In young embryos the cells may be rearranged by manipulation of the tissue, but on fixation the fibrils are continuous.

4. The process of fibril formation can be followed under the microscope.

5. The possibility of "washing out" a non-coagulated colloid from the meshes of a network can be eliminated by fixing the tissues under the microscope.

6. The form and structure of the network varies with the fixative.

7. Cut pieces of tissue placed in contact and fixed show a continuity of fibrils.

8. Intercellular jelly washed out and passed through a filter can be precipitated as a complete network with the ordinary fixatives.

9. Complete washing out of the intercellular jelly gives a fibrillar-free picture when the tissue is treated with fixatives, while the filtrate can be made to precipitate as a fibrillar network.

10. Digestion methods do not show the fibrils unless some step in the technique involves a coagulating or dehydrating process.

11. Complete and similar fibrillar networks can be obtained by the action of fixatives on pure solutions of gelatin, mucin, plasma, egg-albumin and other solutions.

12. While the density of the network increases with the age of the tissue, the process is reversed when post-mortem digestion or acidosis is allowed to proceed. The state of the colloid at the time of fixation determines the type of fibrils.

13. Cells may move freely in certain embryonic stages, and sections show no track left by the passing cell in among the fibrils.

14. In fixed and sectioned tissue the cells and their processes and fibers show by their alignment the evidence of pressure or pulls. The "fibrils," however, radiate in all directions unchanged and do not show stress lines.

The consideration of connective tissue and neuroglia fibrillae as fixation artifacts is of aid in accounting for the following phenomena :

1. Movement of cells. Diapedesis. (The pathway is a structureless jelly.)

2. Progressive increase in strength with age, from the jelly-like younger embryos to the tougher adult tissues.

3. Non-appearance of fibrillae in the living, with their appearance in fixed tissue.

4. The variation in the fibril pattern when different fixatives are used.

5. The similarity of pattern of fibrin in the blood-vessels and fibrillae between the cells.

6. The similarity of many of the staining reactions of the fibrillae and fibrin. Those stains which stain the mucoid element serve to differentiate.

7. Accommodation of the connective tissue to the invading cells of growing organs.

8. The appearance of isolated, fluid-filled spaces lined by endothelium in the connective tissue.

9. Variation in the behavior of successive sections or "similarly" treated pieces of tissue when subjected to pancreatic digestion.

10. "Superiority" of fixed tissue over fresh tissue for demonstrating "fibrillar structures of frameworks of organs" by means of digestion methods.

11. The variation of behavior of fibrils to Bielschowsky's silver method.

12. The appearance of fixed tissue of cells, much smaller than when alive, apparently fading out into fibrillae.

13. The clear-cut lines of separation when connective tissue shrinks away from the more solid cell masses on fixation, leaving a few fibrillae bridging the gap.

14. The stickiness of living connective-tissue substance and connective-tissue cells.

15. The increase in density of the fibril network with age. The more concentrated a colloid, the thicker the network that is formed on precipitation.

16. The varying observations on basement membranes.

17. The appearance of ribbon-like fibers in the fresh, which turn into a thick network of fibrils on fixation.

18. The appearance of neurogliar fibrillae ("cell processes") extending into trophospongia of nerve cells. The pecipitation of the intercellular colloid is a simpler explanation.

The fibers of adult tissues are formed by the thickening (concentration increase) of the colloid lying between the fibroblasts. The polarization of the cells, their movement and the stress exerted on the growing tissue, all serve to give the adult white fibers their arrangement as strands in a bundle. This method of fiber formation enables us to understand the shrinkage which accompanies fibrosis in the tissues. If we accept the fact that a less dense colloid leaves lighter fibrils than a more concentrated one, then we have a means of telling the consistency of tissues when the fixed sections are studied. A physiological determinant is also supplied, directing the distribution of new capillaries along the lines of least resistance.

LITERATURE CITED

Baitsell, 1915   The origin and structure of a fibrous tissue which appears in living cultures of adult frog tissues. Jour. Exp. Med., vol. 21, p. 479.

Bell, 1909. On the histogenesis of adipose tissue of the ox. Am. Jour. Anat., vol. 9, p. 420.

Butschli, 1892. Mikroscopische Shaume. Leipzig.

Clark, E. R., 1912. Further observations on living growing lymphatics: their relation to the mesenchyme cells. Am. Jour. Anat., vol. 13, p. 360.

Danchakoff, 1908. Untersuchungen uber die Entwicklung von Blut und Bindgewebe bei Vogeln Arch. f. mikroscopische Anatomie u. Entwicklungsmechanik, Bd. 73, S. 147.

Ferguson, 1911. The application of the silver-impregnation method of Bielschowsky to reticulai and other connective tissues. Am. Jour. Anat., vol. 12, p. 277.

Ferguson, 1912. The behavior and relation of living connective-tissue cells in the fins of fish embryos, with special reference to the histogenesis of the collaginous or white fibers. Am. Jour. Anat., vol. 13, p. 129.

Fischer, A., 1899. Fixirung, Farbung und Bau des Protoplasma. Jena, S. 34-36.

Fischer, M. H., 1915 Oedema and Nephritis, 2nd ed., New York, p. 210

Flemming, 1897. Quoted from Schafer: Text-book of Microscopic Anatomy, 11th ed., New York, 1912.

Flint, 1903. The connective tissue of the salivary glands and pancreas with its development in the glandula submaxillaris. Johns Hopkins Hospital Reports, vol. 12, p. 8.

Hansen, 1899. Über die Genese einiger Bindgewebsgrundsubstanzen. Anatomische Anzeiger, Bd. 16, S. 424

Hardesty, 1904. On the development and nature of neuroglia. Am. Jour. Anat., vol. 3, p. 254

Hardy, 1899. On the structure of cell protoplasm. Jour. of Physiol., vol. 14, p. 187.

Höber, 1914. Physikalische Chemie der Zelle und der Gewebe. Leipzig and Berlin, S. 313.

Holmgren, 1904. Über die Tropospongien der Nervenzellen. Anatomischer Anzeiger, Bd. 24, S. 225

Huntington, 1910. The phylogenetic relations of the lymphatic and blood-vascular systems in vertebrates and the genetic principles of the development of the systematic lymphatic vessels in the mammalian embryo. Anat. Rec., vol. 4, p. 1

Isaacs, 1916. Properties of colloids in relation to tissue structure. Anat. Rec., vol. 10, p. 517

Isaacs, 1917. The reaction of the kidney colloids and its bearing on renal function. Am. Jour. Physiol., vol. 45, p. 71.

Kampmeier, 1912. The development of the thoracic duct in the pig. Am. Jour. Anat., vol. 13, p. 430.

Kaneko, 1904. Künstliche Erzeugung von Margines falciformes und Arcus tendinei. Arch. f. Entwicklungsm, Bd. 18, S. 317.

Mall, 1892. Reticulated tissue and its relation to the connective tissue fibrils. Johns Hopkins Hospital Reports, vol. 1.

Mall, 1902. On the development to the connective tissues from the connective tissue syncytium Am. Jour. Anat., vol. 1, p. 331

Mann, 1902. Physiological histology, Oxford, p. 196

Maxinow, 1906. Über die Zellformen des Lockeren Bindgewebes. Arch. f. mikroskopische Anatomie, Bd. 67, S. 683.

McClure, 1910. The extra-intimal theory and the development of the mesenteric lymphatics in the domestic cat. Anatomischer Anzeiger, Bd. 37, S. 101.

Meves, 1910. Über Structuren in den Zellen des embryonalen Stutzgewebes, sowie über die Entstehung der Bindgewebsfibrillen, insbesondere derjenigen der Sehne. Arch. f. mikroskopischen Anatomie, Bd. 71, S. 149.

Moody, 1910. Some features of the histogenesis of the thyroid gland in the pig. Anat. Rec., vol. 4, p. 429.

Posner and Gies, 1904. A preliminary study of the digestibility of connective tissue mucoids in pepsin-hydrochloric acid. Am. Jour. Physiol., vol. 11, p. 350.

Ranvier, 1889. Quoted from Schafer: Text-book of microscopic anatomy, 11th ed., London, 1912, p. 117.

Ross, 1915. The trophospongium of the nerve cell of the crayfish (Cambarus). Jour. Comp. Neur., vol. 25, p. 523.

Rous and Jones, 1916. A method for obtaining suspensions of living cells from the fixed tissues and for the plating-out of individual cells. Jour. Exp. Med., vol. 23, p. 549.

Schafer, 1912. Text-book of microscopic anatomy, 11th ed., London, 1912, p. 116.

Triepel, 1911. Das Bindgewebe im Schwanz von Anurenlarven. Arch. f. Entwicklungmekhanik, Bd 32, S. 482

AN EXPERIMENTAL INVESTIGATION OF CERTAIN FEATURES OF THE PHARMACOLOGICAL ACTION OF SALVARSAN.*

By D. E. Jackson, Ph. D., M. D., and G. Raap, A. B., A. M.

Cincinnati.

In a series of experiments performed at the Hygienic Laboratory in Washington in the year 1918 it was shown by Jackson and Smith[1] that one of the most important and outstanding features of the acute symptoms of poisoning following the intravenous injection of arsphenamine solutions in dogs consists in the production of a very marked and prolonged rise in the pulmonary blood pressure. This within itself would perhaps be sufficient to account for a part, if not for all, of the milder toxic symptoms which are occasionally produced clinically by the injection of arsphenamine. But aside from the pulmonary vascular changes, there remained the possibility that the dyspnea and marked respiratory disturbances which are frequently present during "nitritoid crises" of severe, acute arsphenamine intoxication might be due to, or associated with, a marked bronchial constriction. This point was not investigated by Jackson and Smith, although at that time the presence of some such factor as this was strongly suspected, particularly on account of the analogy in action on the bronchioles which is often exhibited among metallic salts. In the present work we have carried out some preliminary experiments in order to determine whether or not any true bronchial asthmatic action is produced by injections of arsphenamine.

The solutions used by us have been made up from "salvarsan" as produced by the H. A. Metz Laboratories in New York. Mr. Metz has very kindly supplied us with a quantity of "salvarsan" of lot No. H56. This was a particularly good batch as had been previously shown by laboratory tests and by extensive clinical use. Generally our solutions have been made up to 2 per cent. strength of salvarsan, and the amount of alkali used in neutralizing the dihydrochloride salt has been sufficient to produce the disodium salt, and in most instances a further slight excess of alkali has been added. In a few cases we used mixtures of the mono- and di-sodium salts. Fresh solutions were always made up only a few minutes before they were injected into the animal.

Figs. 1, 2, and 3 show at once the action which salvarsan has on the systemic blood pressure (lower tracing) and on the bronchial musculature. The lung tracings in these experiments were made by means of a special method[2] in which air was intermittently aspirated from the chest cavity while the tracing was made by a tambour connected with the side tube of the tracheal cannula. The dogs were pithed in each case. In tracing 1 it is seen
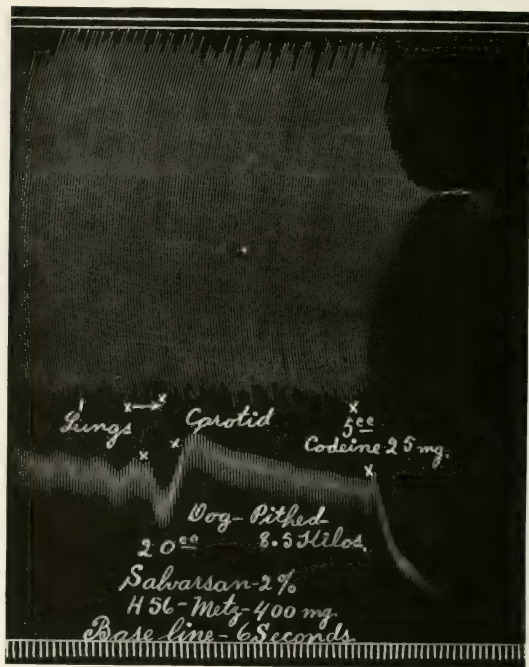
Figure 1.

that 20 c. c. of 2 per cent. salvarsan solution injected into a dog weighing 8.5 kilos produced practically no effect at all on the bronchioles, either in the nature of contraction or dilatation. Fig. 2 shows a moderate contraction of the bronchioles as indicated by the slight reduction in amplitude of the respiratory tracing. (It should be noted here that the pulmonary pressure of this animal undoubtedly rose to a great height following the injection of the salvarsan.) Near the end of this tracing an injection of 4 c. c. of codeine sulphate (20 milligrams) was made. This produced a marked contraction of the bronchioles and was intended to be a check on the technic
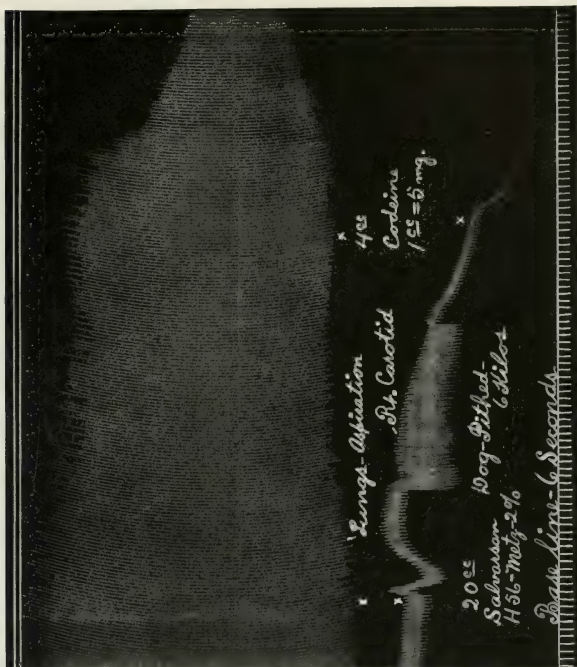
Figure 2.

of the experiment in order to show that the apparatus, the lungs, etc., were all working properly. Fig. 3 is a similar experiment in which 20 c. c. of salvarsan caused a slight dilatation of the bronchioles. These experiments show that *good* preparations of salvarsan do not cause a marked contraction of the bronchioles. But, on the other hand, they do not show that especially toxic preparations might not produce very serious results in this direction. Obviously this point should be investigated further, and with a much larger range of samples of arsphenamine than we have had at our command in the present investigations. A number of intermediary chemical
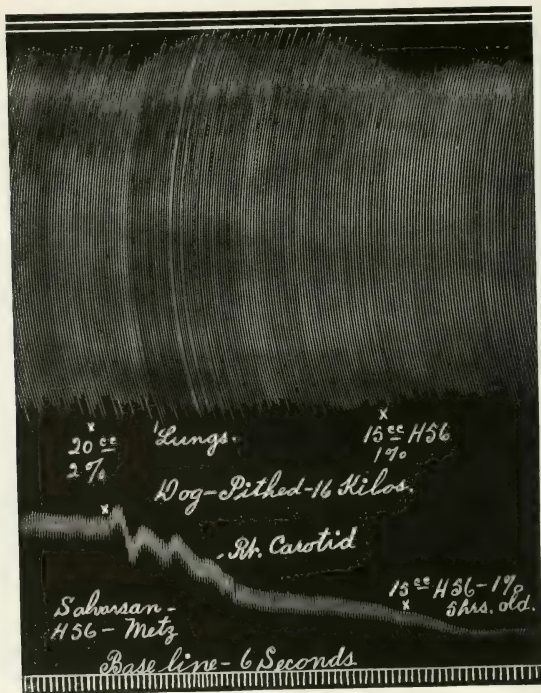
Figure 3.

compounds produced in the manufacture of arsphenamine were examined by Jackson and Smith, but it appeared that none of those examined at that time could be responsible for severe, acute symptoms following arsphenamine injections. But in a later paper by Smith[3] it was shown that another intermediary compound, namely amino-hydroxy-phenyl-arsenoxide, which is an oxidation product of arsphenamine, affected the pulmonary blood pressure in a manner quite comparable with that of a solution of arsphenamine of corresponding strength. "The arsenoxide content of arsphenamine varies

$$As=O$$

$$NH_2$$

$$OH$$

usually between 0.5 and 2 per cent. Occasionally a preparation is encountered that contains as high as 5 per cent. arsenoxide (Dr. C. N. Myers, quoted by Smith) and such a preparation might very readily be highly toxic
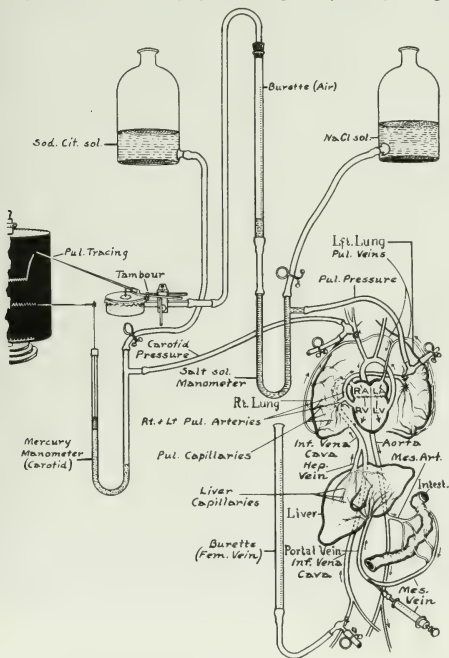
Figure 4.

owing solely to its arsenoxide content." In a recent article by Schamberg, Kolmer and Raiziss[3] the presence in some arsphenamine and neoarsphenamine preparations of an unidentified toxic substance designated by them

as "X" has been emphasized. And Stokes and Busman[5] have reported toxic reactions following injections of arsphenamine through a certain brand of so-called pure gum rubber tubing when this is new, but not after the tubing has been used for a short while. It is obvious that such factors as these might possibly cause a severe, or even fatal, bronchoconstriction in very susceptible patients, when any such constriction was complicated by the
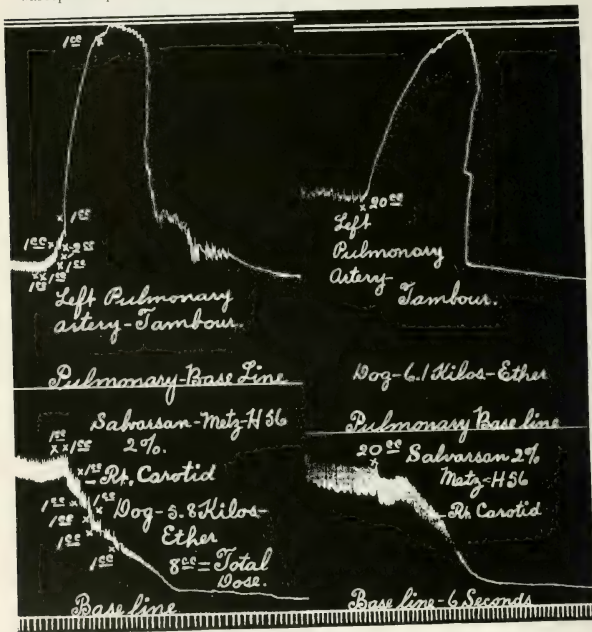
Figure 5.

simultaneous presence of a great rise in the pulmonary arterial pressure. Unfortunately it will require many more experiments before all such obscuring phenomena as these can be fully investigated. But the present experiments have been sufficient to show that any dangerous bronchoconstriction is not to be feared with the proper use of *first-class preparations* of arsphenamine. (See also Hanzlik and Karsner[4].)

Bearing in mind the evident rise in pulmonary arterial pressure after arsphenamine injections, as first demonstrated by Jackson and Smith,[1] and which was further investigated by Smith[3] alone, we have attempted in the present work to investigate further certain features of this important reaction. We have accordingly devised a very sensitive method for detecting very minute changes in the pulmonary pressure. The arrangement of the
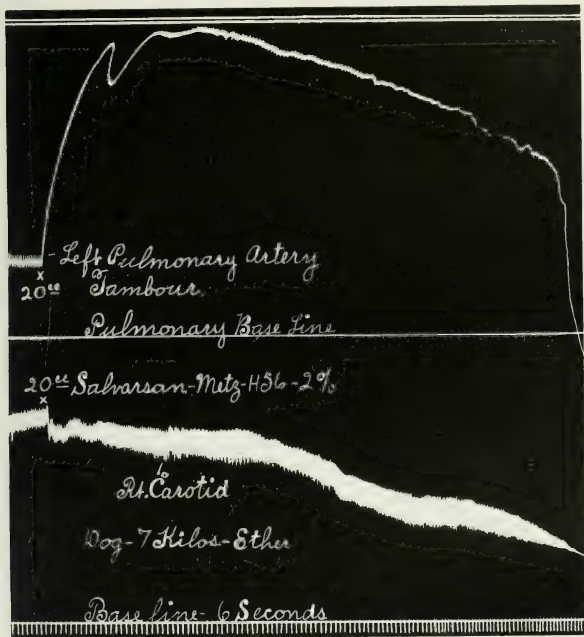
Figure 6.

apparatus as used by us is diagrammatically illustrated in Fig. 4. In this illustration it will be seen that a cannula tied into the left pulmonary artery was connected with a manometer by rubber tubing. The chest was opened widely and artificial respiration was maintained throughout the experiment. Ether was administered by means of a special sight-feed device[6] which has

been described by us elsewhere. The manometer and the rubber tubing connecting with the pulmonary artery were all filled with normal salt solution (0.8 per cent. sodium chloride in water). This solution has worked very well for us, and clotting has been very much less troublesome than was the case when we used sodium citrate solution. This latter is very poisonous and easily stops the heart if a small amount gets back into the right ventricle. Sodium chloride solution does not affect the heart. The top of the distal limb of the manometer was connected by rubber tubing to a burette of 50 c.c. capacity. The salt solution reached only a little way up in the burette, the upper part of which contained air and was connected by means of glass and rubber tubing to a tambour having a bowl about two inches in diameter. The tambour was very sensitive and thus readily recorded on the drum very minute changes in the pulmonary pressure. Carotid pressure was recorded in the usual manner with a mercury manometer.

Fig. 5 shows the results in two different dogs of injections of salvarsan solution, as recorded from the pulmonary (upper) and carotid (lower) arteries. It will be seen that the pulmonary pressure rose abruptly to a great height and that it did not fall until the carotid pressure reached a very low level. In the left hand tracing only 8 c.c. in all was injected into a small dog, yet this killed the animal. In the right hand tracing 20 c.c. of solution was fatal.

Fig. 6 shows a profound and lasting rise in pulmonary pressure following injection of 20 c.c. of 2 per cent. salvarsan solution. It will be noted here that the carotid pressure remained at almost the normal height for a considerable time after the injection of the drug, which was carried out rapidly. And again the pulmonary pressure remained very high until the heart had reached an extremely weakened condition.

From Figs. 5 and 6 it will be seen that sudden intravenous injections of salvarsan produce their chief circulatory results primarily in the lungs. From a clinical standpoint it is interesting to speculate as to what symptoms such an action as this might produce in the patient. And Fig. 6 shows further that an ordinary blood pressure determination as recorded from the arm might prove very deceptive so far as showing the real condition of the entire circulatory system was concerned. For here the general systolic pressure had *fallen* only a few millimeters at a time when the pulmonary pressure had *risen* to an enormous height. It will be noted, of course, that the dose and rate of injection here considerably exceeded that applying clinically. We have accordingly attempted to get some comparative insight into the matter by giving very small, consecutive injections as shown in Fig. 7. In this case 1 c.c. was injected and then, after an interval, a further 1 c.c. etc., was given. In this manner we are able to observe the immediate results following each separate small dose. It is seen that 1 c.c. causes a very considerable rise in pulmonary pressure. The second 1 c.c. dose still further increases this rise, as does each of the succeeding injections. And it will

be seen that the systemic pressure actually rose following the first injection. Five injections of 1 c.c. each and one injection of 3 c.c. (8 c.c. in all) finally brought the pulmonary pressure almost to the limit of its capacity to rise. And this process represented a duration of some minutes.

Figs. 5, 6 and 7 all well illustrate a peculiar phenomenon which appears to be always present in experiments involving the rapid injection of salvarsan solutions. It will be noted that in each of these tracings the pulmonary tambour at the very beginning of the record exhibited marked excursions
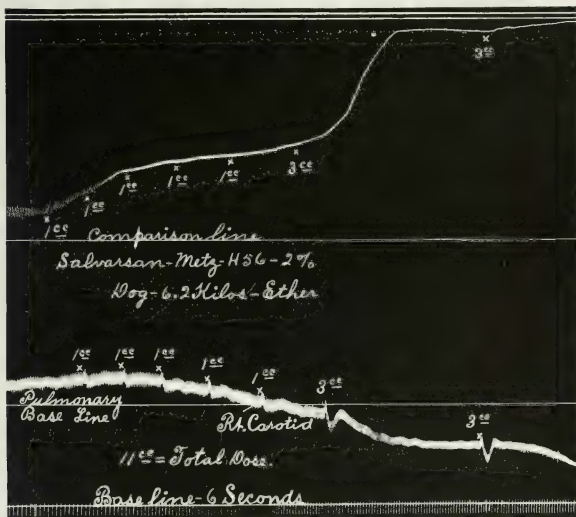
Figure 7.

up and down. These excursions resulted from the respiratory movements of the lungs. The corresponding excursions can also be seen in the mercury manometer tracing from the carotid pressure. The speed of the drum was too slow here to show the blood pressure movements following each individual beat of the heart. But immediately after the injection of the drug the pulmonary pressure started to rise. At the same time the amplitude of the respiratory excursions of the tambour began to decrease, and as soon as a very high altitude was reached by the pressure the respiratory

excursions were reduced to a minimum or disappeared altogether. But during all this period the respiratory inflation and deflation of the lungs remained constant, for this was carried out by means of an artificial respiration machine. Now let us ask, What is the cause of this peculiar change in the pulmonary blood pressure as reflected from the respiratory excursions of the lungs? For we have noted above that but little change was produced in the bronchial musculature by the salvarsan.
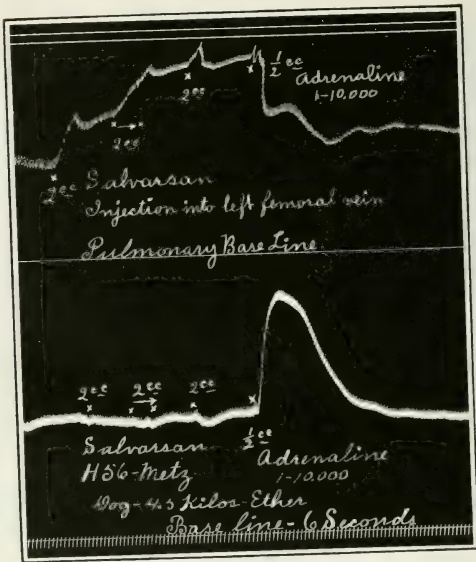
Figure 8.

Fig. 8 probably illustrates a point having a bearing on this subject. In this tracing it is seen that three small injections of 2 c.c. each, produced a marked rise in the pulmonary pressure but had only a slight effect on the carotid pressure. Following these, however, an injection of ½ c.c. of adrenaline (1-10,000) was given and this raised the carotid pressure but markedly lowered the pulmonary pressure. At the same time there was a slight tendency for the amplitude of the respiratory movements of the pulmonary tambour to increase, that is, to return toward the normal again. But as the

effects of the adrenaline wore off the respiratory excursions of the tambour again became reduced. This same point is again illustrated, perhaps more markedly, in Fig. 9. This peculiar and unexpected action of adrenaline calls to mind at once the various clinical recommendations which have been made by Milian,[7] Beeson,[8] and others regarding the use of adrenaline in cases of severe arsphenamine poisoning. And the relation which adrenaline bears to the spasmodic contraction of the bronchioles in acute anaphylaxis
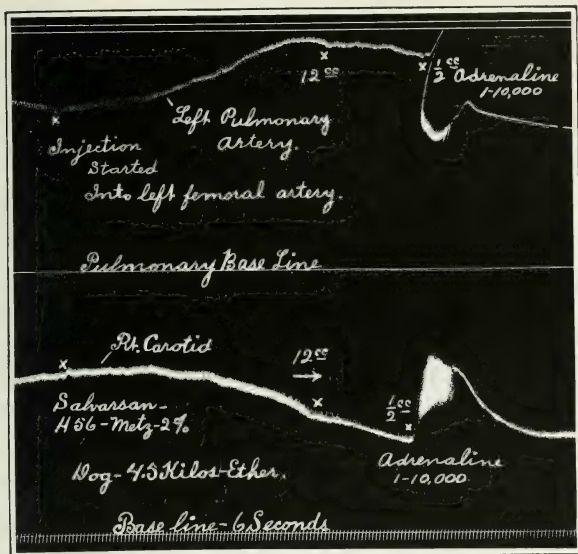
Figure 9.

also reminds one of the various anaphylactic hypotheses by which different writers have attempted to explain the cause of arsphenamine poisoning. We have not been able to prove, however, that the phenomena which we have noted here as being produced by adrenaline in cases of experimental acute salvarsan poisoning bear any direct relation to the clinical results which have been described as being produced by adrenaline injections in some cases of arsphenamine poisoning. On the other hand, the apparent improvement

and lowering of the pulmonary pressure would undoubtedly be of benefit in these cases. We strongly suspect that the lowering of the pulmonary pressure here was due to a mechanical shifting of the blood from the venous to the arterial side of the circulatory system. This would result from contraction of the arterioles. The direct action of adrenaline on the heart would also tend to improve the general character of the circulation. It would appear that when the pulmonary pressure is very high, then the pul-
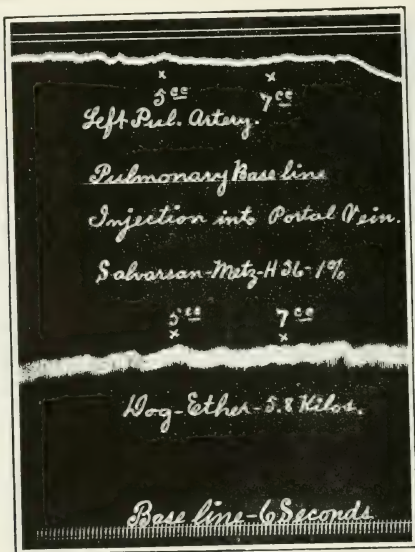
Figure 10.

monary arterioles, etc., are put on such a high tension that the regular respiratory movements of the lungs are not sufficient to cause much change in the relative movement and volume of blood in the pulmonary vessels, as indicated in the tracing made by the pulmonary tambour. Adrenaline causes a general shifting of the blood volume and thus indirectly affects the pulmonary pressure.

We wish now to take up another phase of the subject. It was long ago shown by Joseph[9] that acid solutions of arsphenamine could produce precip-

itation in the blood if the concentration of the drug exceeded 0.1 per cent.
And Danysz[10] has attempted to show that precipitation of the arsphenamine
occurs both *in vitro* and *vivo* even with alkaline solutions. Smith,[3] in the
light of these and other previous observations, has carefully studied this
point with reference to the action of solutions of arsphenamine on serum
in vitro. He finds that acid solutions (dihydrochloride) of arsphenamine
produce very bulky precipitates in serum *in vitro*, and also cause a great
rise in pulmonary pressure if injected intravenously. *In vitro* the precipi-
tate between serum and the monosodium salt of arsphenamine varies from
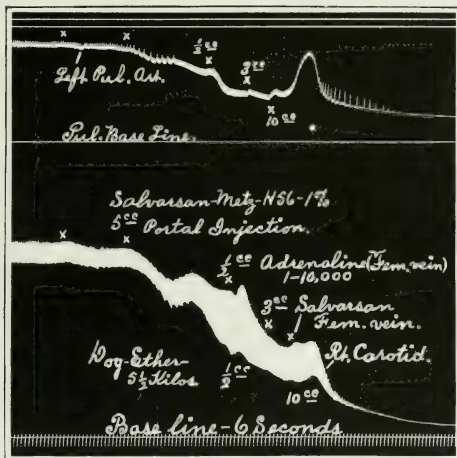
Figure 11.

a distinct turbidity to a moderately heavy precipitate. But Smith found that
no precipitate occurred *in vitro* between dog serum and alkaline arsphena-
mine solutions containing 0.8 c.c. or more normal sodium hydrate per 100
mg. of drug. Smith has also shown further that perfusion of the lungs with
a solution of arsphenamine dihydrochloride in physiological salt solution
causes a contraction of the pulmonary vessels and a consequent decrease in
the rate of outflow of the perfusion fluid. Since this occurs with acid
arsphenamine solutions, it seems evident that the drug itself acts directly
on the pulmonary arterioles to cause contraction, and that this is not entirely
dependent on the alkali of the solutions as ordinarily used. Apparently then

pulmonary vascular obstruction may be due to an extensive precipitate of the drug, to a specific action of the drug itself on the muscle fibers of the arteriole walls, and to the presence of alkali in the solution used. In order to throw some further light on this question we have made injections of the drug into the femoral artery as shown in Fig. 9. In this case it will be seen that a dose of 12 c.c. produced a considerable rise in the pulmonary pressure. (The rise was really about twice as great as the curve shows, for a slight leak in the metal bowl of the tambour was allowing air to escape very slowly throughout the tracing. This was discovered after the experiment was over.) We believe that in this case the drug (injected into the peripheral end of the femoral artery) simply washed out the blood from the artery and
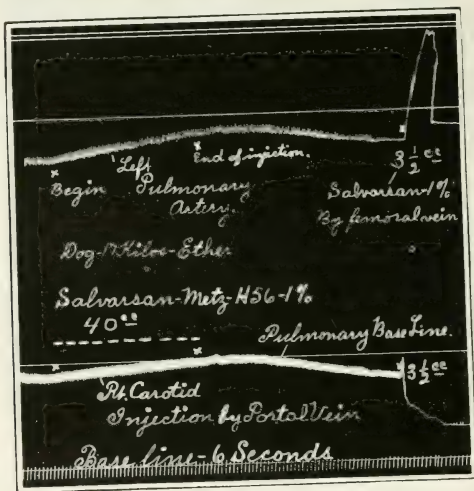
Figure 12.

then passed directly on into the femoral vein without being precipitated out to any marked extent in the leg capillaries. This then, was almost equivalent to slow injection into the femoral vein directly.

We next proceeded to inject the salvarsan solution into a branch of the portal vein. In this case the solution had to pass through the liver capillaries as shown diagrammatically in Fig. 4. Fig. 10 shows the result of two such injections (of 5 c.c. and 7 c.c.). It will be noted that no rise occurred

in the pulmonary pressure, but on the contrary some slight fall may have been produced.

Fig. 11 shows first an injection of 5 c.c. of salarsan solution into the portal vein of a small dog. This produced an obvious fall in both the pulmonary and the carotid pressures. Following this ½ c.c. of adrenaline solution was given. This caused a slight fall of pulmonary pressure, but only a faint rise of the systemic pressure. As a check on the action of the apparatus, etc., two other injections (3 c.c. and 10 c.c.) of salvarsan solution were finally given *by way of the femoral vein.* The latter of these produced a very obvious rise in the pulmonary pressure. These experiments evidently show that the liver has removed from the salvarsan solution its power to cause a rise in the pulmonary pressure. But on the contrary some portion of the drug must pass through the liver and on into the general circulation, for Fig. 11 shows that the salvarsan injections caused the systemic pressure to fall to zero and thus caused the death of the animal. This same point is further illustrated in Fig. 12. Here 40 c.c. of 1 per cent. salvarsan solution was injected (between the points marked x, x). This dose by femoral vein would certainly have raised the pulmonary pressure to a great height. Here, however, only a gentle rise in the pulmonary pressure was produced, and this appears as if it might have been due simply to the addition of solution to the blood volume of the animal. But nevertheless, this dose of the drug still exercised a very obvious toxic action on the animal. Near the end of the tracing an attempt was made to inject salvarsan into the femoral vein. Three and one-half c.c. were injected which started to produce an immediate rise in the pulmonary pressure, but unfortunately some air passed into the vein through the injecting cannula and the animal died of air embolism (verified at autopsy). The marked rise in the pulmonary tambour here, however, serves as a valuable check on the technic of the experiment and shows that any rise which the salvarsan might have produced in the pulmonary pressure would have been promptly recorded. We feel obliged to conclude, therefore, that if salvarsan solutions be injected into the portal vein, the passage of the drug through the liver will almost, if not totally, remove its power to raise the pulmonary pressure. It is probable that this action occurs to some extent, and this may be rather marked in some instances, in the case of the arterioles and capillaries of the leg also. But the liver seems to be much more effective in this direction than are the tissues of the leg.

It seems probable to us that this action of the liver results mainly, if not entirely, from a precipitation of the major portion of the salvarsan within the organ itself, perhaps in the form of emboli in the liver capillaries. The well-known detoxicating action which the liver manifests toward many poisons is not probably extensively concerned in this matter, at least not in the manner in which such detoxication is usually considered. There is a rather striking significance in the rapidity with which this precipitation must

occur in the liver, if this is the correct explanation, for evidently only a very small proportion of the pulmonary pressure raising substance passes the liver, while at the same time very obvious effects from the drug may be produced in the carotid pressure immediately. This point perhaps has a bearing on the marked symptoms of liver disturbance, jaundice, etc., which are frequently manifested clinically in arsphenamine poisoning.

CONCLUSIONS.

1. First-class preparations of salvarsan have almost no direct action on the bronchial musculature of the dog. It seems obvious that acute symptoms resembling anaphylactic shock, or the so-called "nitritoid crises," if produced by *good* preparations of salvarsan cannot be due to a spasmodic contraction of the bronchioles. But we are not sure that this action might not occur in the case of especially toxic samples of the drug.

2. We have studied the action of salvarsan on the pulmonary pressure by means of an especially sensitive method. We believe that even the smallest injections of salvarsan exercise some immediate action on the pulmonary pressure. Its detection depends only on the sensitivity of the method employed for its investigation.

3. When the pulmonary pressure has been greatly raised by salvarsan we have noted that injections of adrenaline tended to lower this pressure, and also to restore the excursions of the pulmonary pressure due to the respiratory movements of the lungs, when these had been previously greatly reduced by the salvarsan. We believe this results mainly from a mechanical shifting of the blood from the action of the adrenaline on the systemic vasculature.

4. When solutions of salvarsan are injected into the general circulation by way of the femoral artery the pulmonary blood pressure is still raised by the drug. But the rise in pressure is less than if the drug were injected by the femoral vein.

5. When solutions of salvarsan are injected into the portal vein and are thus carried through the liver before passing into the general circulation, then it is found that the drug produces but little if any effect on pulmonary pressure, although if the dosage is very large the pulmonary pressure may be raised slightly, apparently only as the result of an increased volume of fluid in the vessels. But toxic doses thus injected tend to lower the pulmonary pressure.

6. We believe this action of the liver is brought about by a precipitation of the drug in the capillaries and arterioles of the liver. This apparently does not correspond to the ordinary detoxicating action of the liver as manifested on many poisons.

7. This precipitation in the liver takes place quickly and it does not prevent some portion of the drug from passing on into the general circulation.

For the systemic pressure may fall to a proportionately much greater degree than does the pulmonary pressure.

REFERENCES.

1. Jackson, D. E., and Smith, M. I.: Jour. Pharmacol. and Exper. Therap., 1918, xii, 221.
2. Jackson, D. E.: Jour. Pharmacol. and Exper. Therap., 1914, vi, 57. Experimental Pharmacology, 1918, C. V. Mosby Co., St. Louis, p. 287.
3. Smith, M. I.: Jour. Pharmacol. and Exper., Therap., 1920, xv, 279.
4. Schamberg, J. F., Kolmer, J. A., and Raiziss, G. W.: Am. Jour. Med. Sc., 1920, clx, No. 2, p. 188. See also Raiziss, G. W., and Proskouriakoff, A.: Chemistry of Arsphenamine and Its Relation to Toxicity, Arch. Dermat. and Syph., 1920, ii, No. 3, p. 280. Kolmer, J., and Lucke, B.: Pathologic Changes after Arsphenamine and Neo-arsphenamine, ibid., p. 289. Roth, G. B.: Toxicity of Arsphenamine and Neo-arsphenamine, ibid., p. 292. Stokes, J. H.: Therapeutics of Arsephenamine, ibid., p. 303. Stetson, D. D.: Permanent Solution of Arsphenamine, ibid., p. 324. Hanzlik, P. J., and Karsner, H. T.: Jour. Pharmac. and Exper. Therap., 1919, xiv, p. 425; ibid., 1919, xiv, p. 375.
5. Stokes, J. H., and Busman, G. J.: Jour. Am. Med. Assn., 1920, lxxiv, No. 15, p. 1013.
6. Jour. Lab. and Clin. Med., 1920, v, 745.
7. Milian: Les intolérants du 606; Bull. Soc. franc. de dermat. et syph., 1912, xxiii, 529. L'administration de l'adrénaline. Paris Méd., 1918, 2 février.
8. Beeson, B. B.: Am. Jour. Syph., 1919, iii, p. 129.
9. Joseph, D. R.: Jour. Exper. Med., 1911, xiv, 83; ibid., p. 179.
10. Danysz: Ann. de l'Inst. Pasteur, Paris, 1917, No. 3, p. 114.

A CASE OF CANCER OF THE VAGINA, CERVIX AND BODY OF THE UTERUS TREATED BY RADIUM.

Howard A. Kelly

Baltimore.

Even in these days of easy and constant communication, when our tens of thousands of Aesculapians have one and all become devotees of the peripatetic philosopher, surgery still advances as heretofore through the ideas developed in sundry pregnant centers where dwells the great man. From the time of Joseph Ransohoff's activities from the early eighties on, Cincinnati has been recognized as one of these fruitful centers, a source of emanations of great ideas in the surgical field. His work is especially characterized by its catholicity, embracing as it has gynecology—see his paper on "Two ovariotomies in the same patient" (1885)—his work on the anatomy of the cecum and appendix (1888), when appendicitis was just beginning to attract attention; his brain surgery, his hernia work, his gall-stone operations, and

No. 1. Photomicrograph showing tissue removed by curettement of uterus before radium treatment. A. indicates invasion of epithelioma into uterine wall.

above all, what attracted my own attention the most, his splendid contributions to the surgery of the kidney, when that important organ was still a *terra incognita* for the average surgeon.

Aside from his distinguished and widely recognized qualities as a surgeon, Dr. Ransohoff was one of the pioneers of this country in the recognition of the value of radium as a therapeutic agent, either co-operative with surgery or substituting it or yet again operative in cases where surgery is impotent. A large experience thus enabled him soon to lay down the rules of dosage and application so difficult in this new field, where so much danger lurks in overdosage. I refer particularly to such publications as:

Radium Treatment of Cancer (with J. L. Ransohoff), Lancet-Clinic, 111, 661 (1914).

Radium Treatment with Uterine Cancers (with J. L. Ransohoff), Ann. of Surg., 64, 298 (1916); Trans. Am. Surg. Assn., 34, 202 (1916).

Radium Treatment of Uterine Fibroids, Lancet-Clinic, 115, 116 (1916).

The following case illustrative of an extensive cancer of the cervix, uterus and vagina, with the sketches and sections made in the course of the treatment and progress towards recovery, is reported as one of the interesting and remarkable examples of the potency of this newest and most
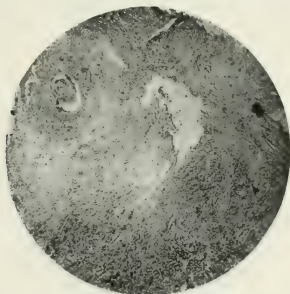
No. 2. Photomicrograph showing tissue removed by curettement ten weeks after radium treatment. The hyaline tissue is typical and follows heavy radiation. Note complete absence of epithelium and the thick wall of the blood vessel in the upper left hand portion in the midst of the hyaline tissue glands.

wonderful of all our remedies, in the field which Dr. Ransohoff has cultivated with such assiduity and success.

The patient, J. H. M., No. 5902, a woman 56 years old, consulted me January 20, 1920, complaining of bloody vaginal discharge, pain in the back, pelvis and limbs, loss of weight and bladder irritability.

Her family history was negative. Past history: Health always good; no serious illnesses; no operations; menstrual history normal; menopause at 48 with no symptoms. Marital history: Five children, all spontaneous deliveries.

Present illness: In the spring of 1917 patient noticed a slight intermittent leucorrhea which gave her no particular trouble until April, 1919, when it became constant and at times blood-tinged. This became more profuse, and from August, 1919, on, it was bloody. In November, 1919, she began having pain in her back, radiating into the pelvis and limbs. About the same time she noticed bladder irritability with constant desire to void. For the past three or four months there has been progressive weakness.

General physical examination negative except for some pallor and evidence of recent loss of weight. No enlarged lymphatic glands anywhere.

Pelvic examination: Vagina short; pronounced rectocele; cervix at first touch appears normal, but on closer examination it is softish and nodular, the anterior lip more involved than the posterior—the anterior lip is fused with the anterior vaginal wall and there is a submucous thickening extending from the junction of the cervix and anterior wall to the orifice of the urethra. The uterine body is somewhat enlarged; there is no evidence of lateral disease, or thickening in either broad ligament. On with-

drawing the gloved hand there is quite a little bloody discharge. Inspection in the knee-chest posture shows a submucous thickening extending over the anterior lip of the cervix down on to the vaginal wall. There are several little granular areas which bleed easily on touch. Protruding from the cervical canal there is a fringe of friable tissue. Examination under anesthesia confirmed without adding to the above findings. Dilatation and curettage showed a cervix enlarged, easily dilated, filled with friable tissue which, when curetted, leaves a crater. The body of the uterus was packed with the same friable tissue. Tissue from both cervix and body of uterus showed a basal cell epithelioma.

Treatment: On account of the extensive local uterine involvement and the definite extension over the entire anterior vaginal wall, radium was advised in preference to operation.

On January 30, 1920, she was given 1208 millicuries screened with 2 mms. of brass and 1 mm. of rubber for three hours and forty minutes—three-fourths of the treatment distributed on three areas in uterine cavity and one-fourth in cervical canal.
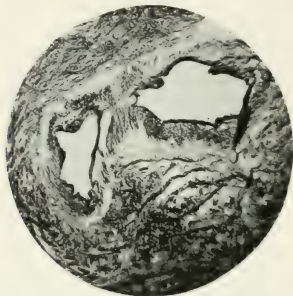
No. 3. Photomicrograph showing tissue removed by curettement nine months after radium treatment. This shows the end result following radiation. Note the fibrous tissue and the distended glands.

Patient was a little nauseated from the treatment, but no more upset than she was following the dilatation and curettage. She returned home on February 2.

She came back on April 15, 1920. All of the bloody discharge had stopped the second week in February. Since then there has been a scanty, serous discharge. She has had no pain, and has gained several pounds in weight, and appears to be in splendid health and is stronger—in fact, she has none of her former symptoms.

A pelvic examination showed the cervix contracted, perfectly normal, absolutely freely movable in every direction—uterine body upright, a little enlarged but perfectly freely movable. There was a slight bloody discharge after examination. Inspection showed the cervix normal. The anterior vaginal wall was also normal, and palpation shows no extension on the anterior vaginal wall. Curettage of the uterine cavity obtained a little necrotic tissue, the curet quickly reaching a firm, fibrous, grating face. Microscopic examination of tissue showed hyalinized fibrous tissue with no epithelial cells.

On September 24, 1920, patient had gained in weight, strength and in every way. Has had a troublesome leucorrhea for the past two months, but no bleeding. Has been having some neuritis in limbs and is neurotic and apprehensive.

Pelvic examination shows vagina negative as to any evidence of disease. Cervix normal, senile, atrophic. Uterus upright, not definitely enlarged. In contact with the vagina there is a sensation of resistance posterior on the right. Per rectum this thickening is definitely felt with the finger, but it is more like that which is due to simple lack of flexibility of the tissues rather than disease. There is no evidence of metastasis in iliac or inguinal glands. On dilatation there is a discharge of pus and on

27 I 1920

Extensive carcinoma
of body, cervix
and anter vaginal
wall.
Curettage left cervix
a crater

CARCINOMA

vag.

No. 4.
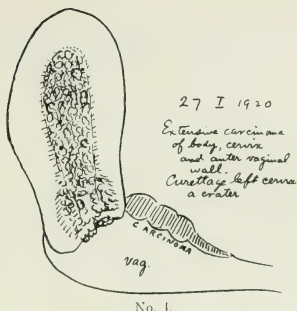
curettement a necrotic material (pyometra) is obtained—curettement quickly reached a firm, muscular base. Curettings examined microscopically showed only radiated tissue.

After this examination was completed and the patient was reassured that there was absolutely no evidence of the old trouble, she was much relieved and during the rest of her stay suffered little from the neuritis which she complained of at home.

15 IV 1920

Carcinoma
Entirely gone

vag.

No. 5.

NOTE.—All these slides were made immediately at the time of the examination, and are frozen sections stained with hematoxylin and eosin. It is of great importance to know that permanent and satisfactory slide records can be made in this way, thus saving much laboratory labor as well as delay. This method of immediate examination emanated from my laboratory, where it was first worked out by Dr. Thos. S. Cullen. It has now been widely adopted in Europe as well as at home. It is, however, not generally known that it obviates, in many cases, further section cutting, as here.

THE DIAGNOSIS AND TREATMENT OF DIAPHRAGMATIC PLEURISY: WITH REPORT OF CASES.*

By T. H. KELLY, B. S., M. D.,

and

H. B. WEISS, A. B., M. D.

Cincinnati.

For many years it has been noted that not infrequently a pneumonia begins with symptoms resembling acute abdominal disease, particularly in children. J. P. Crozer Griffith[1] reported several cases, as did also Herrick[2] and others. Needless to say, many clinicians have suffered the experience of advising operation for some acute intra-abdominal condition, only to find the abdominal contents normal and a pneumonia in one of the patient's lower lobes the day following the operation.

To Capps[3] we owe the well-defined picture of involvement of the diaphragm by inflammatory processes. He published in 1911 the results of experimental irritation of the diaphragmatic pleura in a series of human beings, the work being done upon patients with pleural effusions. Irritation of the diaphragm was accomplished by means of a wire introduced through a trocar inserted into the pleural cavity preparatory to the withdrawal of the pleural effusion. His observations covered experiments upon seventy-five patients, only thirty-five of whom presented favorable conditions for free exploration of the diaphragm. He also presented in the paper a very complete discussion of the previous work, which has been published upon the innervation of the visceral and parietal pleura.

He concluded from his experiments that:

1. The visceral pleura is not endowed with pain sense.

2. The parietal pleura is richly supplied with sensory fibers from the intercostal nerves and irritation of it produces pain that is accurately localized by the individual over the spot that is touched. Such irritation never gives rise to "referred" pain in the neck or elsewhere.

3. The diaphragmatic pleura receives its nerve supply from the last six intercostal nerves, which supply a peripheral rim of the diaphragm two or three inches wide anteriorly and laterally and a segment corresponding to the posterior third, and from the phrenic nerve which supplies the central portion of the diaphragmatic pleura.

The pain produced by irritation of the central part of the diaphragmatic pleura is a true referred pain, and is distributed over the skin and tissues supplied by the third and fourth cervical segments, with a predilection for the trapezius ridge.

The pain elicited by irritation of the peripheral or posterior portion of the diaphragmatic pleura is also a true "referred" pain. The pain is usually

distributed in segmenta areas over the lower thorax and epigastrium, some-times extending downward over the whole abdomen on the same side (seventh to twelfth dorsal segments).

Both pains are spontaneous and are associated with hyperesthesia and hyperalgesia of the skin and superficial tissues on pressure.

4. The pericardial pleura receives its innervation chiefly, if not exclusively, from the phrenic nerve. Irritation of this part of the pleura results in "referred" pain in the neck of the same character as that following irritation of the central portion of the diaphragmatic pleura.

This work offered a definite starting-point from which to work in the diagnosis of involvements of the diaphragmatic pleuræ, and in 1916 Capps[4] published a series of sixty-one cases of diaphragmatic pleurisy, in all of which the diagnosis was confirmed either by autopsy or the subsequent history of the cases. In this article he called attention to the various distributions of the referred abdominal pain, and emphasized the points of difference between it and the pain of true abdominal disease.

The skin and muscles of the abdomen are more sensitive in referred pain from the diaphragmatic pleura than in abdominal visceral disease, and the cutaneous reflexes are more lively in referred pain. Deep pressure with the flat hand is better born in referred diaphragmatic pain, while it produces deep pain over an inflamed organ within the abdomen.

The presence of sharp localized pain in the neck, occuring spontaneously or only on pressure, on the same side as the abdominal pain often suggests the true state of affairs, as it indicates irritation of the phrenic nerve. The referred pains in the neck and abdomen are often aggravated by cough or deep breathing.

Also, in acute diaphragmatic disease there are usually present evidences of respiratory infection, such as cough, expectoration, herpes labialis, rapid respiration, high leukocytosis, etc. According to Capps, hiccough is not common in diaphragmatic disease, as was formerly supposed, having occurred only five times in his sixty-one cases.

The differential diagnosis of involvement of the diaphragmatic pleura and abdominal disease is very important, and at times the clinician is in a veritable whirlpool of indecision concerning the correct diagnosis. We have had the opportunity in the past two years of observing in the Cincinnati General Hospital and the Wilhelm and Gette Beckman Dispensary a number of patients exhibiting some or all of the features mentioned by Capps in his dscription of diaphragmatic pleurisy. In certain of these cases the question of surgical intervention was quite acute and the importance of correct diagnosis therefore correspondingly great.

From these cases we have selected twenty-two in which the diagnosis was confirmed either by their future course or at the autopsy table, and are presenting them, hoping to show the variations in the manifestations of diaphragmatic pleural disease and the different paths by which we arrived

Number	Sex	Age	Hyperesthesia and hyperalgesia	Abdominal	Neck	Beneath twelfth rib	Elsewhere	Hiccough	Acute	Chronic	Nausea	Vomiting	Friction sounds	Pneumonia	Temperature	White blood cells	Polynuclears, per cent.	Roentgen rays
1	M.	48		X	X	X	Over dorsal spinous processes	X	X X		X			X	100.4	22,000	Increased	Definite
2	F.	15		X	X	X			X						100.4	20,000	93.0	Definite
3	M.	26		X	X	X	Over dorsal spinous processes		X				X	X	101.6	20,000	88.0	Definite
4	E.	55		X	X	X			X				X		103.6	11,800	68.0	Not definite
5	M.	40		X	X	X			Exacerbation				X		98.6	5,500	77.5	Definite
6	M.	40		*					X	X					99.0	4,100	79.0	Not definite
7	E.	31		X		X						X			99.0	8,900	80.0	
8	M.	39		X					X	X				X	105.0	12,800	70.0	
9	M.	36		X	X	X				X				X				Definite
10	M.	45			X	X				X					99.6			Definite
11	M.	45			X	X												Definite
12	M.	41	X															Not definite
13	E.	23	X	X	X	X				X	X	X			101.2	13,200	54.0	Definite
14	M.	38	X	X	X	X			Exacerbation				X		100.0	13,500		Definite
15	M.	38	X	X	X	X							X		102.6	15,200	Increased	Not definite
16	M.	35	X	X	X	X			X	X			X		99.0	8,900	Increased	Definite
17	E.	44		X	X	X			X						99.0	12,300	70.0	Definite
18	E.	43		X	X	X			Exacerbation 13+						101.6	9,600		Definite
19	M.	46		X	X	X			X	X					101.6	6,800		Definite
20	F.	38		X	X	X		X					X		101.0	14,200		Fourteen definite
21				X	X										99.2			
22				X	X													
Summary			7	19	19	17		2	3 exacerbation 13+	9	2	2	7	5				

*Doubtful

at a diagnosis in the different instances. The table on page 4 shows the symptoms, both subjective and objective, that were found in our cases. (See Figs. 1, 2, 3.)
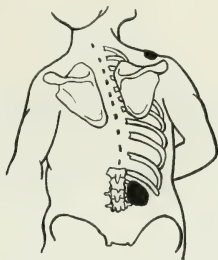
Fig. 1, Case 1. Showing points of tenderness along the trapezius and beneath the twelfth rib posteriorly.

Of these twenty-two cases, ten were acute in character, three had acute exacerbation at the time of observation and nine were subacute or chronic. The following cases in the first group resembled surgical conditions so closely that the question of operative intervention was seriously considered:
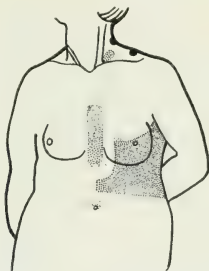
Fig. 2, Case 2. Showing points of tenderness along the trapezius, in solid marking, and the stippling showing areas of hyperesthesia and hyperalgesia.

No. 1, renal stone; No. 4, acute cholecystitis; No. 6, cholelithiasis with colic; No. 8, generalized acute peritonitis from perforated typhoid ulcer; No. 14, operation was done for an acute appendicitis, much to our chagrin; Nos. 18 and 22 both had operation for gall-bladder disease several years

previous to the time of observation. In both cases neither stones nor any other pathological condition were found at operation, and shortly afterward there was a recurrence of the symptoms that had existed before the opera-
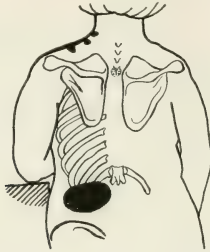
Fig 3, Case 3. Showing points of tenderness along the trapezius posteriorly and tenderness beneath the twelfth rib and an area of hyperesthesia over the fourth dorsal spinous process.
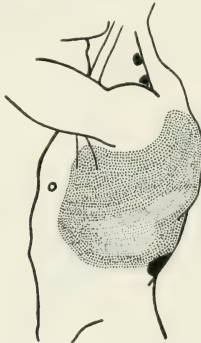
Fig. 4, Case 12. A lateral view showing areas of hyperesthesia and points of tenderness along the trapezius and beneath the twelfth rib posteriorly.

tion. In the remaining cases of the acute group the symptoms or history immediately gave an inkling as to where the seat of the trouble lay.

In the group of chronic types the question of surgical treatment arose in No. 7, which is interesting because it combined definite symptoms of diaphragmatic pleurisy and a chronic appendicitis, which were both proved by the further history of the case. In the acute cases the symptoms arose sud-

denly, as with the onset of pneumonia, and after several weeks practically all the symptoms had left. On the other hand, in the chronic cases, the onset was acute and the symptoms subsided, but at irregular intervals there was a recurrence of the symptoms, in whole or in part, usually without an increase in temperature and not with the original acuteness. At these periods of recurrence exertion and cough intensified the symptoms, and frequently exertion was the cause of the recurring attack. The chronic sufferers com-
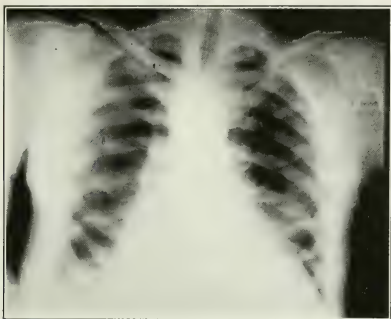
Fig. 5, Case 1. Roentgen-ray plate showing small area of infiltration over left diaphragm.
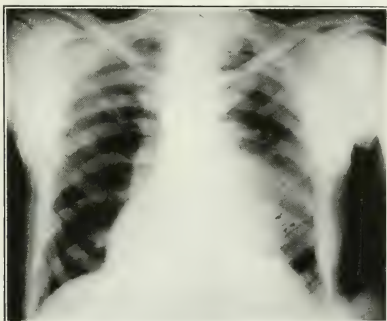
Fig. 6, Case 1. Showing a definite area of infiltration six days after the first picture was taken.

plained just as bitterly of the pain and, occasionally, of the hyperesthesia as those who suffered from an acute attack.

Hyperalgesia and hyperesthesia were not always marked, being present in seven cases. The hyperesthesia, when present, was most acute, and one
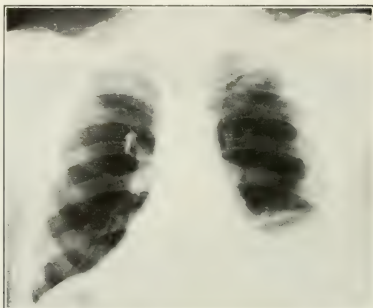
Fig. 7, Case 6. Showing the position of the diaphragm and markings of the right lower base. One month after this plate was taken another pair of stereoscopic plates "failed to show the shadows at the right base which were seen on the previous plates."
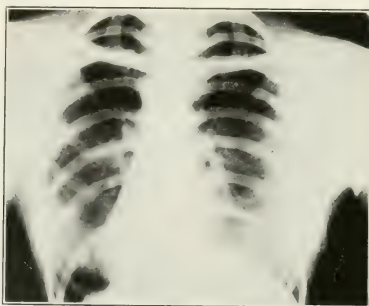
Fig. 8, Case 13. Showing distortion of the left diaphragm by adhesions

of the patients cried out when the tips of the fingers were passed over the skin. In one patient clothing was almost unbearable. The involvement in hyperesthesia was usually over a large area. (See charts.) Hyperthesia

and hyperalgesia were much more apparent in the acute than in the chronic cases as a rule. In the great majority of cases deep abdominal pressure was borne quite well. Spontaneous pain was not always present in the neck when pain on pressure was marked.

The two most constant areas of tenderness on pressure were below the twelfth rib posteriorly on the affected side and at the ridge of the trapezius, though the patients did not always complain of spontaneous pain at these points. The upper quadrants of the abdomen were the most frequent sites of the referred abdominal pain. In many of the cases the abdominal pain radiated toward the flanks, and in two of them there was definite tenderness, involving the entire half of the back from the lower ribs to the ilium. There was usually moderate rigidity and muscle spasm of the abdominal muscles at the areas of referred pain. Abdominal symptoms of varying degree were present in nineteen of the twenty-two cases. In two cases there was board-like rigidity over the abdomen. One was operated for relief of acute appendicitis and the appendix was found apparently innocent of any disease. In the other case (No. 8) the rigidity and muscle spasm continued until there appeared definite signs of consolidation in the left base. This is the only patient who died, and at autopsy the pathologist reported: "In the left pleural cavity there were a few acute fibrinous adhesions over the left lower lobe and no fluid. The pleural surface of the left side of the diaphragm was congested and had about its middle point and extending posteriorly from this a small amount of fibrin, some of which was undergoing organization. Beneath this and surrounding it there was exceedingly well-marked venous congestion. The peritoneal surface of the diaphragm showed nothing but slight congestion. The lower lobe of the left lung showed a diffuse lobar consolidation, and all of the bronchi of this lobe were filled with pus. There were no abnormal findings in the abdomen."

Capps states that in his series of sixty-five cases hiccough appeared in only five cases, while in our twenty-two cases this symptom occurred in two cases, and in both was quite intractable, all of the usual methods for its relief failing, the hiccoughs apparently ceasing spontaneously.

Fourteen of our cases were males and eight were females. Gastric symptoms were not frequent. One case showed both nausea and vomiting, while nausea and vomiting were present, each once, in separate cases. In seven cases friction sounds were heard, practically all in the lower axillary region of the affected side. These friction sounds were probably due to an associated involvement of the costal pleura. Five patients had pneumonia associated with their pleurisy. In the majority of the acute cases there was a rise in temperature, though not very high. The leukocyte count was increased, depending on the acuity of the symptoms as a rule; associated with the increase in leukocytes there was a proportionate rise in the polymorphonuclear neutrophile cell count.

In but four of the nineteen cases examined by the Roentgen rays there were no findings suggestive of pleural or pulmonary involvement. The Roentgen-ray finding varied, ranging from definite distortion of the diaphragmatic contours to merely a definite increase of the hilum markings radiating to the border of the diaphragm. In several instances, shadows suggesting calcification were lying close to the diaphragm. In two of the accompanying reproductions of Roentgen-ray plates one can see in the early picture a finger-like infiltration above the diaphragm and in the latter picture the shadow of a definite infiltration of the lung in the same region.

The diagnosis of diaphragmatic pleurisy was usually made on the occurrence of pain in the side, associated with pain beneath the twelfth rib on the affected side and along the edge of the trapezius on that side. The pain may be spontaneous in the neck and was so in one-third of our cases. In nineteen out of twenty-two cases there was tenderness along the edge of the trapezius. There is almost a constant finding of tenderness on pressure beneath the twelfth rib posteriorly on the affected side; this symptom was present nineteen times in twenty-two cases. In the vast majority of the cases there is referred pain in the abdomen, with varying degrees of muscle spasm and rigidity. A moderate rise in temperature with an increase in the leukocytes and polymorphonuclear cells is usually present. In some cases there are heart friction sounds in the lower axilla.

The Roentgen-ray examination of the chest in over three-fourths of the cases did *show* definite diaphragmatic involvement or pulmonary involvement close to the diaphragm.

In chronic cases there is exacerbation of the characteristic symptoms on exertion, cough and frequently on deep inspiration.

Treatment. In the acute cases the treatment is that of any pleuritis. We have found that cold applications, in the form of iced-linen strips, applied (and frequently changed) to the affected side for two hours, is most efficacious. Of course, sedatives are used when necessary. Strapping the lower chest and upper abdomen seems to give the greatest relief, and many of our chronic cases return to us asking that their sides be strapped. They have found that after the side has been strapped their pains will be relieved almost immediately and that they will be free from their annoying symptoms for from several weeks to months.

We are indebted to Mr. R. Isaacs for the accompanying charts.

BIBLIOGRAPHY

1 Griffith: Jour. Am. Med. Assn., 1903, xi, 531.
2. Herrick: Jour. Am. Med. Assn., 1903, xi, 535.
3. Capps: Arch. Int. Med., 1911, No. 6, viii, 717.
4. Capps: Am. Jour. Med. Sc., 1916, No. 3, cli, 333.

DEMONSTRATION OF THE INTERVENTRICULAR MUSCLE BANDS OF THE ADULT HUMAN HEART.*

By H. McE. Knower

Cincinnati.

This demonstration is made on a specimen of adult human heart in which the fat, coronary vessels and epicardium have been removed to expose the superficial muscle fibers of the ventricles and of the conus. This superficial sheet is cut on the posterior surface to the left of the posterior interventricular groove (sulcus longitudinalis posterior), and the right ventricle rolled away from the left after the method followed by J. B. Macallum with pig embryos' hearts. The septum is thus split open, exposing the inner terminations of the muscle bands which arise superficially from the right and left atrio-ventricular rings, and from the conus, and end in the papillary muscles of the left ventricle. Deeper fibers are also shown, extending from the left ring to the large papillary muscle of the right ventricle, and from the conus to this papillary muscle. The membranaceous septum is split, showing the position of the atrio-ventricular bundle of His in a novel and striking manner. The septal blood-vessels are also found readily. The right and left ventricles may be thus unrolled further until opened from the septal side, as done by Macallum for young pig hearts. A fair proportion of hearts taken from dissecting-room subjects, preserved by injection of carbolic, glycerin, alcohol solution and afterward kept for a time in cold storage or in vats of weak carbolic, are found to be suitably macerated for this demonstration.

The results of Winkler, Pettigrew, Ludwig, Krehl and Macallum are thus readily examined in the human heart; we believe for the first time.

It is urged that students should be induced to study the heart in this way, after working out the coronary circulation, etc., rather than to simply cut open the ventricles after the method used by the pathologist in autopsy, since these cuts destroy the important muscle connections. The tracing of the muscle bands between the right and left ventricles will furnish a valuable aid to the better appreciation of the action of the heart. The relations of the papillary muscles to the interventricular (and conus) muscle bands can hardly be understood without this dissection.

OCULAR ANGIO-SCLEROSIS.*

By George H. Kress, B. S., M. D.

Los Angeles.

THE TERM ANGIO-SCLEROSIS.

Ocular angio-sclerosis, as a term to indicate the hardening or over-growth of connective tissue of the walls of the blood-vessels of the eye, is perhaps a better term under which to group the type of changes to be here discussed, than to refer to the process either as arterio- or phlebo-sclerosis, although it must be confessed that the term arterio-sclerosis, through common usage, conjures up the most definite conception to the minds of many of us.

The study of sclerosis of the vascular system is especially interesting to ophthalmologists, because in the eye, as nowhere else in the body, do we find an organ with terminal arteries where many of the changes in the structure of the blood-vessels can be thoroughly examined from day to day.

VASCULAR SCLEROSIS CLOSELY ASSOCIATED WITH FAULTS OF OUR CIVILIZATION.

The close association of sclerosis of the vascular system with some of the major faults and vices of our civilization, such as over-eating, high tension living (both mental and physical), alcoholism, and syphilis; and its intimate connection with chronic nephritis (perhaps as often a precursor as a corollary of the last-named disease) ; as well as with the fault of simple old age (a condition most of us aspire to in spite of its defects and disadvantages), even though we are less disposed to accept that of our heredity, a causative factor also to be reckoned with; and the further fact that vascular sclerosis more often manifests itself after the age of forty, at which time most persons have occasion to seek the services of an oculist; and that a careful examination of the fundus at that period may give important data at just the time when there may be few other clinical symptoms of arterio-sclerosis elsewhere, should make this subject one of equal and of very considerable interest to eye specialists and to general practitioners alike.

ANGIO-SCLEROSIS A GRAVE DISEASE.

General arterio-sclerosis is a condition not to be permitted to go on to terminal or very frank stages, if health and life are to be conserved; and ocular angio-sclerosis, not alone because of its capacity to impair vision, but because the changes of the sclerotic process are in the eye sometimes earlier or more evident than in other portions of the body, can therefore, be the means of earlier diagnosis and proper treatment; and through its early recognition we may be in a position to prolong the life of a considerable number of our patients.

OCULAR ANGIO-SCLEROSIS FREQUENT PAST THE AGE OF FORTY.

Hirschberg, in a series of cases of old persons coming to him for refraction, found evidence of retinal angio-sclerosis in 50 per cent., and microscopic examinations of the retinal vessels of old people show, according to Hertel, an even higher percentage of sclerotic involvement than this.

HYPERTENSION A FREQUENT CONCOMITANT OF ANGIO-SCLEROSIS: AND THE NEED OF DETERMINING WHETHER HYPERTENSION EXISTS.

Since the sclerotic changes are so often associated with hypertension of the vascular system, the question suggests itself as to whether it should not be a routine practice for eye specialists to take the blood pressure of all patients seeking refraction about the age of forty and after; to the end that a special effort may be made to obtain an exact record of the condition of the ocular vascular system in such persons as give evidence of increased blood pressure. The fact that an increased general blood pressure so discovered may also enable us the better to guard against glaucoma, is likewise important to eye specialists.

Increased vascular blood pressure has also been noted in connection with cataract, and even though it is not possible to stop this lens change, appropriate treatment may, before cataract extraction, somewhat reduce the danger of post-operative hemorrhage.

The fact that it is still a matter of discussion as to whether vascular hypertension is or is not antecedent to vascular sclerotic changes, need not concern us, since we are in possession of the important fact that nearly always this hypertension is one of the early manifestations or concomitants of vascular sclerosis; although it must be remembered that there be those who believe that in this early stage, a hypotension may alternate with a hypertension (the latter construed to be dependent at this stage upon a spasm of the muscular coats of the arteries).

INTRA-OCULAR GLOBE TENSION MIGHT ALSO WELL BE TAKEN.

In taking these blood pressure readings, it might well be a part of our routine to take also a reading of the intra-ocular globe tension with a Schiötz tonometer or a Gradle or other modification. The tonometer (using 1 per cent. holocain, which is slightly antiseptic, and which does not exfoliate the corneal epithelium, as does cocaine, to anesthetize the cornea) can be quickly used; and the information received from such a tonometer reading is generally conceded to be far more accurate and valuable than that from finger palpation.

THE NORMAL ANATOMY OF THE RETINAL BLOOD-VESSELS.

According to Oatman, in the large central artery of the optic nerve, there can be demonstrated an outer (adventitia) of connective tissue; a middle (or media) of elastic and fibrous tissue, interspersed with a few

muscle elements; and an inner (or intima) made up of (1) an elastic lamina; (2) a subendothelial layer, and (3) a stratum of endothelial cells. As the central artery appears on the disc, however, and its branches get farther away therefrom, the above-mentioned subendothelial layer and elastic layer of the intima usually give place to a few elastic fibres only.

As regards the normal veins, however, in the retinal divisions of the normal central vein, this subendothelial layer, and the so-called elastic membrane of the intima, are lacking; and the retinal veins are, in fact, little more than tubes of fibrous tissue lined by endothelial cells.

THE MORBID ANATOMY OF THE RETINAL BLOOD-VESSELS.

It is not necessary for our purpose to go into much discussion concerning the microscopic morbid anatomy of the sclerosed blood-vessels other than to reiterate that in the arteries, the inner coat shows a thickening, either from patchlike areas of endothelial proliferation, or from a very considerable addition to the subnedothelial connective tissue (the latter more of a fibrosis, and then process most often met with in the veins); the middle coat presenting usually areas of necrosis and hyaline and fatty degeneration, with formation of atheromatous *detritus,* which may or may not be later on infiltrated with calcareous material. The outer coat in more advanced cases may also show thickening, but whether this is due to the circulating toxins or is only an evidence of compensatory thickening or protection of the vessel wall, is not yet determined.

In phlebo-sclerosis, the intima likewise shows the increase of connective tissue in the internal coat, and the degenerative changes in the outer layers, with a weakening and widening thereof, or if calcareous deposits be associated, then a stiffening or hardening of the vessel.

These facts concerning the normal and abnormal anatomy of the retinal blood-vessels should be borne in mind in any consideration of the changes which take place in ocular angio-sclerosis.

HOW THE INTERNAL EYE TUNICS SUFFER THROUGH ANGIO-SCLEROSIS.

As a result of the angio-sclerotic changes, the eye tunics are supplied by blood-vessels with narrowed lumina and bathed with blood containing the toxic elements lying at the root of the sclerosis. Consequently, the nutrition and metabolism of the retinal and other ocular tissues suffers. Associated with the above factors are the weakened vessel walls and their greater tendency to leak and be responsible for hemorrhagic spots in the retina.

THE EFFECTS OF ANGIO-SCLEROSIS ON VISION.

Sudden diminution of vision of marked amount does not, however, usually result from angio-sclerosis, except when the sclerotic changes occlude the lumen of the central artery or vein; or, with more extensive weakening of the ocular vessels, are responsible for a sudden intra-ocular hemorrhage.

A weakness in the visual power in persons past forty, which does not respond to suitable refractive correction, should, however, lead to a suspicion of vascular changes, and indicate a close examination of the retinal vessels to see if such changes can be discovered.

SYSTEMIC SIGNS OF ANGIO SCLEROSIS ALSO WORTHY OF NOTE.

In these patients in whom arterio-sclerosis is suspected, it is well also to have the blood pressure taken, and the heart examined to determine whether a hypertrophied left ventricle is associated with accentuation of the aortic second sound, or increased intensity of the first sound, or whether there is any displacement of the apex beat. A careful and periodical examination of the urine should also be made.

If the picture of retinal angio-sclerosis be at all advanced, even though the general signs of arterio-sclerosis, be not prominent, the possibility of concurrent cerebral arterio-sclerosis, with its danger of apoplexy, should be kept in mind.

CLINICAL STAGES OF SYSTEMIC ANGIO-SCLEROSIS.

Just as in tuberculosis we deal with three stages of incipient, intermediate, and terminal involvement, so also in vascular sclerosis do we find a beginning stage, difficult of recognition; an intermediate stage, with franker signs; and a terminal stage, in which the involvement is so general as to nullify much of our attempted therapy. It is in this third or last stage also that patients are seen in whom a steadfast hypo- may succeed a previously persistent hypertension.

PECULIARITIES OF THE EYE STRUCTURE IN RELATION TO OCULAR ANGIO-SCLEROSIS.

Without further comment, we can now pass on to a consideration of ocular angio-sclerosis proper, simply again calling attention to the fact that in the eye, we are dealing with terminal or end arteries of very delicate structure, with little or no arrangement for compensatory circulation (although with the retinal veins there is more provision for a collateral circulation), so that endovascular irritants have full opportunity to make their power felt; and, further, that because of the structure of the eye, we can use our dark room instruments in making close and systematic observation of these changes, the handicap being not always that the changes are not present, but that in our haste we fail to note them.

SUBJECTIVE MANIFESTATIONS OF OCULAR ANGIO-SCLEROSIS.

Among subjective phenomena may be noted early decrease in the power of accommodation, or severe headache persisting after refraction has been corrected at the onset of presbyopia. The subject of diminution of vision has already been discussed.

OBJECTIVE SIGNS OF OCULAR ARTERIO-SCLEROSIS.

Among the objective manifestations are the following:

General: Arcus senilis;

Slow reaction of the pupil;

Hyperæmic optic disc of dull-red color;

Œdema of the retina (patches more often in the vicinity of the disc or blood-vessels).

Course of arteries: a tendency to cork-screw course in one or more arteries, especially the smaller arteries and veins near the disc.

Number of arteries: a seeming increase in the number of smaller retinal vessels, due to dilatation making them visible to the eye.

Pressure effects of arteries: a disposition on the part of the harder arteries to flatten out the veins somewhat, at the places where the arteries cross the veins; or it may be that the course of the vein at such a crossing, where it can ordinarily be traced beneath the artery without loss of continuity, is lost until it reappears on the other side of the artery.

Light streaks on arteries: an increase in the brightness of the light streak (the so-called "silver wire" appearance). Other streaks on arteries: with perhaps an associated continuous, or interrupted and somewhat nodular whitish streak of lesser brightness outside the vessel walls (this appearance being in the retinal peripheral vessels in contrast to the occasionally seen congenital connective tissue sheath of vessels which is limited largely to the disc area), these perivascular streaks being due to an infiltration in the lymph sheaths of the vessels, or to the fact that the usually transparent vessel walls in their now thickened state reflect more light from the blood stream than formerly.

Color and translucency of arteries: a decrease in the color and translucency of the vessel walls.

Locomotion pulse: with these changes may be present the so-called "locomotion," or arterial pulse, not dependent upon pressure, as in glaucoma. Such a pulse is often best seen where the arteries bend sharply.

Venous pulsation: in advanced retinal arterio-sclerosis, because of the hardened blood-vessels, digital pressure on the eyeball may fail to bring out venous pulsation or blanching of the vessels.

Calibre of arteries: while the arteries are not often widened in the earlier stages of retinal arterio-sclerosis, later on they may become narrowed. The larger arteries, or veins, of the optic disc at times show some of these changes best.

Disc margin appearance: in addition to the above, the optic disc and the larger retinal vessels may be surrounded by a greyish haze.

Hemorrhagic spots: where the disease has made greater progress, blood extravasation may occur near the vessels, ranging from dots and short streaks to real blotches of hemorrhage.

OCULAR ANGIO-SCLEROSIS A DISEASE AFFECTING BOTH ARTERIES
AND VEINS; AND FURTHER SIGNS IN RELATION TO
SOME OF THE PHLEBO-SCLEROTIC CHANGES.

The changes noted above may not only involve veins as well as arteries,
but also, to a certain extent, may be almost limited to the veins. This seem-
ingly larger involvement of the veins in ocular than in general vascular
sclerosis, may be explained in part perhaps because in the eye we can watch
minute changes in the vein, size, course, etc., which because of less firm
anatomical structures than the arteries, are less discernable through coarse
finger palpation, etc., in other portions of the body.

In the veins, also, there may be the picture of constriction and dilatation
in different portions of the same vein.

If a hardened artery press firmly on a vein beneath, there may be dila-
tation in the portion of the vein in the periphery of the fundus; while the
part next to the disc is narrowed. The pressure of the artery helps the
tendency toward the phlebitis, which is already present as a result of the
basic causes of the angio-sclerosis.

If the vein walls weaken only in spots, then in lesser degree, the veins
may show the bulbous varicosities seen in other parts of the body.

With more advanced phlebities, and the secondary constriction of the
vein lumen, spots of adjacent hemorrhage appear often also.

BOTH INTRA- AND EXTRA-OCULAR HEMORRHAGES OF SIGNIFICANCE
AS REGARDS ANGIO-SCLEROSIS.

In connection with retinal hemorrhage, it is well to remember that in
intra-ocular blood extravasation that cannot be otherwise accounted for,
occuring in persons about the age of forty or after, such a sign should always
suggest thorough examination of the blood pressure of the individual. To a
certain extent, this same suggestion applies to so-called idiopathic subcon-
junctival hemorrhage and œdema of the lids.

AN EARLY RECOGNITION OF OCULAR ANGIO-SCLEROSIS IS VERY
IMPORTANT.

These, then, are some of the signs of angio-sclerosis as seen in the eye,
and as stated in the beginning, the gravity of the general disease process, and
the necessity of an early recognition and treatment thereof, warrant a
close examination for such changes in the fundi of all persons coming to us
for refraction about or after the age of forty. By so doing, in a consid-
erable number of instances, it will be possible to conserve the health and
prolong the life of patients who themselves are altogether unconscious of
the serious malady at work within their bodies.

A FEW WORDS ON TREATMENT.

In closing, a few words in regard to treatment may not be amiss. The
early detection of vascular sclerosis is, of course, of great importance, be-

cause then the cause can be sought and an attempt made to prevent its further action.

The very nature of the disease, from the standpoint of causative factors and pathology, necessitates emphasis on the hygiene of living. The life which is indicated to be led by such patients should be one of moderation in work, in eating, in exercise, and in personal habits of life; with emphasis on elimination by bowels, kidneys, skin, and respiratory tracts.

Proper drugs have their place, especially the iodides for their alterative and resorptive effects, while symptomatically the nitrites and sedatives, like the bromides, may be of value. The digitalis and strychnine groups can also be called upon if the heart condition indicates their exhibition.

But in any rational therapy, the elimination of the underlying causes of the sclerosis are, of course, of the greatest importance, and in conjunction with the above measures, cannot be too much emphasized.

BIOLOGIC ASPECTS OF DEMENTIA PRÆCOX.*

F. W. LANGDON, M. D.

Cincinnati.

When the genius of Kraepelin—genius being here, as usual, simply a synonym for a high order of painstaking work—"merged," under one name, a group of psychoses characterized in common, by development in adolescence, emotional apathy, poverty of thought, inadequacy of volition, and progressive or intermittent deterioration, he conferred a lasting benefit on the student of mental disorders and the sociologist.

This "master stroke of a master mind," however, did much more than furnish a convenient formula for diagnosis and prognosis; it suggested at once the possibility of a common cause or causes for the disease process; and presented for solution the problems of its possible biologic significance and pathologic interpretation.

In brief, what does it mean in terms of normal and perverted life?

These deeper problems are not only important—they are of *vital importance*—to the civilized nations of the earth as well as to such as may attain civilization in the future. Their consideration therefore is timely, particularly to us of the United States of America, the "melting pot of the nations," where "preparedness" is the watchword, and may be the price of continued liberty of, and government by, the people.

To illustrate this point of view, we have only to realize that one-fifth of the total discharges from our army in 1912 was for mental disease (not including neurasthenia and hysteria). "The discharge rate for mental disease per 1000 was 2.64; higher than for any other class of disease; tuberculosis, including all its forms, being next with a rate of 1.56 per 1000."[1]

The same writer states that "more than half the mental diseases with which we meet in the United States Army, requiring asylum treatment, are of the one form, dementia præcox."

Now, if our present army, composed of picked material of a "good" physical and mental standard, develops 2.64 per 1000 of cases of mental disease per year, what may we expect of the "1,610,600 men available for military duty," in the state of New York for instance, according to the report of the adjutant general of New York in 1915?[2] Were these organized into a military body, the number "weeded out" in one year on account of mental disease, based on the above figures, would be 4250; more than *four full regiments* "killed" without firing a shot; and of these more than *two whole regiments* would be victims of dementia præcox.

It is evident that these figures, based on a proportion of 50 per cent. of dementia præcox in admissions from the army to the Government Hospital for the Insane, are higher than those of the general population, which range

---

from 15 to 25 per cent. in different states. But it must be remembered that the *army* is recruited from "picked" material as regards *age* as well as physique and mentality, and consequently consists of men of a "dementia præcox age," in much greater proportion than does the civil population.

There is no reason to believe that the situation in European armies is any better—if as good.

It is not only the material for armies that is involved in the question of dementia præcox, but the general population at a most productive time of life.

It must not be supposed, however, that we of the United States of America are alone in facing this problem. Our friend and fellow-member of this association, Dr. Frederick Peterson[3] of New York, writes me: "Dementia præcox is probably as common in Japan as elsewhere." This opinion is based on his own extensive observations in that country. He also writes me:[4] "I saw cases of dementia præcox among the native Fellaheen in Egypt. . . . I remember perfectly a typical case in a Sudanese negress."

(Photo. by Dr. W. H. R. Stoddart.)

Fig. 1. Chimpanzee: Hand showing *flat* thenar eminence and *pad* of thumb directed forward. (Compare Fig. 4.)

My friend Dr. S. Lilienstein,[5] of Bad Neuheim, German, a psychiatrist of large experience in Germany and the Orient, also informs me that—

In China and Japan in general there are the same kinds of mental diseases as in our asylums (of German). In Japan . . . I saw, for instance, many cases of hebe-phrenia or dementia præcox, imitating the voices of animals, and it was explained to me that they fancy themselves to be "bewitched" into beasts, wolves, dogs, or hens.

In connection with the foregoing we must remember that the Egyptians represent the remains of one of the oldest civilizations, in a state of regression, while Japan is an example of an also ancient civilization, which has taken on within a half-century most tremendous evolutionary stride.

The case noted in a Sudanese negress, by Peterson, near the other point of the scale, indicates that dementia præcox is not necessarily a disease of higher civilization, while it may be more common in such.

The biologic significance of the foregoing may be postulated, for our present purpose, as follows:

(1) The efficiency in the "struggle for existence" of races and nations will be adversely affected in proportion to the mentally deficient of all types,

contained in their populations. Of these dementia præcox is of the greatest importance because of its numerical preponderance and of its incidence at the most ambitious and productive period of life, when the foundations are being laid for the highest achievements of the race, as well as its perpetuation.

Hence, the chances for supremacy, or inferiority, or even the very existence of a nation or race, may hinge, in the future, upon its proportionate population of subjects of dementia præcox.

Turning from these matters of racial and national biologic bearing to those of individualistic significance—what evidence have we which may throw light on the fundamental nature of dementia præcox?

Three views are current with respect to the underlying processes of the disorder, which is evidently more than a mere psychosis.

First: That it is due to some unknown toxin or toxins of specific character to this disease and producing no other. Such toxin may act directly on the nervous mechanism through the nutrient fluids or indirectly by disturb-

Fig. 2. Chimpanzee: Hand showing *non-rotation* of terminal phalanx of *thumb*, during flexion.

(Photo. by Dr. W. H. R. Stoddart.)

ances of organs of internal secretion. In the latter case by producing a secondary "endocrinopathy."

There is nothing in the nature of the disorder inherently opposed to the "specific disease" hypothesis, which is held by eminent investigators—among them Kraepelin[6] himself. It must be admitted, however, that, until recently, evidence of an accepted pathologic nature has been lacking and clinical observation is not satisfying.

The recent extremely important researches of Southard,[7] however, with his findings in 90 per cent. of fifty cases, of "evidence of general or focal brain atrophy or aplasia, when examined post-mortem, even *without* the use of the microscope"—throw a strong light on this aspect of the disease. Southard's investigations and conclusions are so remarkable for wealth of detail as well as conciseness of statement that no abstract could do justice to them—and the reader is therefore referred to the original. His conclusion is that dementia præcox must be removed from the class of *functional* psychoses and placed with the *structural* diseases.

Secondly: There is the view of Stoddart, Mott, Adolf Meyer,[8] Hoch[9] and others, that in the dementia præcox patient, we are dealing with an organism inherently defective in make up, or of incomplete evolution which is unable by reason of such incompleteness to effect the proper "adjustments" to the increasingly complex conditions of existence, incident to puberty and adolescence. Some evidences pointing in the direction of this solution of the problem are offered on subsequent pages.

The third view rests on the postulate that the defective adjustments, which are obviously present, are due to psychogenic causes, chiefly or entirely. In other words, the organism may be good or fair inherently, but its "psychic mechanism has been accidentally shunted" on to a wrong track by conditions ("conflicts") too complex for its resistance. (Bleuler.[10])

C. Macfie Campbell[11] has contributed a comprehensive and illuminating survey of the subject. If it be permissible to "summarize his summary" the writer would do so as follows:

Many authors . . . have regarded the symptoms as merely the incoherent expression of the disordered activity of poisoned nerve tissue. . . . Meyer (Adolf) has formulated a conception of the disorder which expresses the fact that the psychosis is the culmination of a long-continued period of *unhealthy biological adjustments* in *individuals who are constitutionally* apt to meet their difficulties in an inadequate manner.

(Photo, by Dr. W. H. B. Stoddart.)

Fig. 3. Chimpanzee: Hand showing *non-rotation* of terminal phalanx of *thumb*, during flexion.

The following dictum in the same article (by Campbell) contains, to the present writer's views, the gist of the whole question:

Alienists should surely be the first to recognize that human biology, if it is to embrace adequately the facts of experience, must be psychological; *psychology is not a branch of philosophy, but that department of biology which deals with the most complex reactions.* (Italics by present writer.)

For the sake of brevity and convenience we may designate the three views outlined above as: The "specific disease," the "subevolutional" and the "psychogenic" hypotheses. All are worthy of the most detailed and serious consideration, but the title of the present paper must limit its scope mainly to consideration of the two latter views.

To the writer the second and third postulates seem not only compatible with, but essential to, each other. Reduced to a homely simile, the one says in effect: "The wagon breaks because it is *too weakly constructed* for the load"; the other, "The wagon breaks because *the load has become too heavy.*"

It is a fundamental principle of biology, that we may never comprehend an organism except in relation to its antecedents and environment.

Looking at the dementia præcox problem in this light, what evidence may we find pointing to possible structural and physiological recessions or atavisms, as accounting for the mal-adjustments which characterize its presence.

The human hand, in the evolutionary procession of the ages, has become much more than the mere organ of locomotion and prehension which are its primary functions in the lower vertebrates. By reason of its "adaptability," under cerebral influence, it has become a highly developed instrument of skill and precision. As such, it has needed, and acquired, modification of structure. Such modifications—of *"recent acquirement"*—biologically speaking, are the first to be lost as a result of failures in adaptation (adjustment in general), in accordance with the accepted law of pathologic degeneration, "last to develop, first to decay." It has gradually added to its primary

(Photo, by Dr. E. A. North.)

Fig. 4. Dementia præcox: Showing *flat* thenar eminence, and *"pad"* of thumb directed *forward.*

functions, those of defence and offence, of the hunter, the fisherman, the artisan and the artist; and finally in the higher races, it has developed into an "organ of expression" second only in importance to the facial and ocular musculature.

As such organ of expression it is not only an important adjunct to spoken language in the orator, the actor and the "man in the street," but has even replaced spoken language successfully in the deaf-mute, and more or less efficiently in communication between alien peoples. Its importance in human affairs is recognized in such current expressions as: "The Hand of God"; "the hand, the servant of the brain"; the "minister of reason and wisdom" (Cresollius). We speak of an unusually useful person as "handy to have around." It is not strange, therefore, that in its numerous variations and deficiencies some should tend to be atavistic in type, or indicative of incompleteness in an evolutionary sense.

Complexity of function implies a correspondingly *complex development in structure* in any organ; and as the hand is readily accessible to observa-

tion, it is natural that the attention of astute clinicians should have been attracted to its pecularities in the subjects of various psychic anomalies.

In civilized life, *the hand-shake* is to be viewed as a motor expression of emotional feeling; and as such, of varied characteristics, from the mere formal "touch" of the finger-tips to the hearty hand-grasp of the warm friend in expressing his pleasure at meeting you after a long absence.

As an organ of *emotional language* it is natural that its motor "expressions" should be listless and defective in dementia præcox subjects; and we find that this is the case.

Kraepelin,[12] in his lectures, repeatedly calls attention to the peculiar mode of response of dementia præcox patients to the ordinary salutation of offering the hand.

(Photo. by Dr. W. H. B. Stoddart.)

Fig. 5. Dementia præcox. Non-rotation of terminal phalanx of thumb.

To quote from his clinical lectures:

". . . I may call your attention to the fact that, when you offer him your hand, the patient does not *grasp* it, but only *stretches his own hand out stiffly to meet it.* Here we have the first sign of a disturbance which is often developed in dementia præcox in a most astounding way."

Again, in his 8th Edition,[13] he mentions the "hand-shake" as "cold, clammy, lifeless, heavy, exerting no pressure."

The present writer in demonstrating these peculiarities in his clinics has referred to this "physical sign" as "the Kraepelinean hand-shake." It evidently deserves to rank as a physiological stigma of importance.

To Stoddart,[14] however, is due the great credit for discovery of certain pecularities of a *structural* character in the hands of dementia præcox subjects, which in a measure, may be correlated with this characteristic handshake.

To this type of hand he has applied the designation "Simian"—for obvious reasons. For some of the illustrations of it accompanying this paper the writer is greatly indebted to the kind courtesy of Dr. Stoddart. They are reproductions of photographs taken by himself. This type of hand may be described as follows:

THE SIMIAN TYPE OF HAND OF STODDART.

(1) With the hand open, the fingers and thumb fully extended and the inter-digital spaces closed—*the palmar surface of the thumb faces forward* —on the same plane, or nearly so, as the palmar surfaces of the fingers. (In the normal hand, the palmar aspect of the thumb faces at a right angle to that of the fingers or nearly so.)

(2) When the thumb is flexed *its terminal phalanx does not rotate inward*—or does so in a less degree than usual. (In the normal hand it does rotate inward, thus contributing to greater accuracy and power of apposition of thumb and finger tips.)

(3) The fingers are markedly *hyper-extensible* at the *metacarpo-phalangeal joint*. In some instances they may be "sent backward" to a right
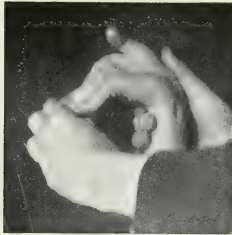
(Photo, by Dr E. A. North)

Fig. 6. Dementia præcox : Showing hyper-extensible fingers at Metacarpo-phalan-geal joints.

angle with the metacarpus. (This peculiarity is also noted in many grown imbeciles and in young children, as well as in the subjects of dementia præcox.)

Since the increasing complexity of structure and function of the hand in man is determined and dominated by a corresponding complexity of the *cortex cerebri*—it is not difficult to correlate a deficiency in hand-structure and function with lack of cortical evolution.

Stoddart[14] comments on these manual stigmata as follows:

These characteristics, taken in conjunction with the facts that they are sometimes encountered in cases of idiocy, especially those of the Mongol type, that imbeciles are liable to develop at puberty symptoms resembling those of dementia præcox, and that the above peculiarities of the hands are also to be observed in the chimpanzee, all points to the conclusion that dementia præcox should be regarded as a failure in evolution, as an atavism or reversion to an ancestral type.

Nevertheless we are bound to admit that atavism does not entirely account for all the features of this disease. The rapidity of the deterioration, the physical ill-health and the possibility of recovery, though rare, all indicate that some active morbid process is at work.

It is apparent from the foregoing that Stoddart inclines to view dementia præcox as a specific disease process developing upon a foundation of sub-evolution or atavism.

Numerous other stigmata of degenerative significance are present in dementia præcox, as those of the face, palate, auricle, etc., but these are common to the subjects of various psychoses—and not especially characteristic of dementia præcox. Hence they do not come within the scope of this paper.

A review of the literature and observation of the diagnostic methods of many psychiatrists, has led the present writer to conclude that these "hand stigmata" are overlooked by a great majority of clinicians—or not given due weight as diagnostic and prognostic indicators.

His personal experience has convinced him of their decided value as factors in diagnosis, especially in that "doubtful" class of cases, sometimes labelled "undifferentiated"—with a prefix of "depression," "elation," ,"hallucinosis," etc., as the case may be.

They are also often of value as guides, in very early stages of dementia præcox; and due consideration of them may make us more guarded in our prognosis in the presence of apparently "mild," "psychic departures."

Some indication of the frequency of occurrence of the "Simian type" of hand in dementia præcox may be of interest in this connection. My associate, Dr. Emerson A. North, has kindly investigated for me a total of forty-four cases, taken consecutively, without selection, in two institutions in Ohio. His results follow:

Simian stigmata:	Typical (+++)	21
	Partial (++)	14
	Absent	8
	*Doubtful	1
		44

The cases classed as "typical" present the *three* chief "stigmata" well developed; namely: Thumb facing forward; absence of internal rotation of its terminal phalanx; hyper-extensile fingers at metacarpophalangeal joint.

Those classed as "partial" presented only *two* of the "stigmata."

In thirty-five cases of forty-four, practically 80 per cent., the stigmata were such as to be of clear diagnostic value.

By way of contrast we may note that the "Simian hand" is rarely seen in typical manic-depressives. The writer has seen a number of patients with "Simian" hands, *diagnosed* as manic-depressives by experienced alienists and has so diagnosed some others himself—on the basis of mental symptoms; but subsequent observation of these patients has shown the original diagnosis to be erroneous, and the course of the disease that of *dementia præcox.*

In addition to the "hand-shake" of Kraepelin, already mentioned, the "snout cramp" of Kahlbaum, noted by Kraepelin, the "shut-in personality"

---

*Observations not trusworthy by reason of extensive deformity of hands by cicatrices of old burns.

of Hoch, the "special make-up" of Adolf Meyer, and other physiological observations, might come up for consideration as of biologic significance, but they are already so widely known and discussed that a mere reference to them is sufficient.

Recently, however, mention has been made of a "sign" of possible biologic bearing, by Steen,[15] which consists in a characteristic sitting attitude, noted by him as "frequent" in dementia præcox subjects and described as follows:

> The arms are held close to the trunk, with, as a rule, the elbow joint in a condition of stiff extension; the hands pronated and resting on the lower part of the thighs, or even on the knees. . . . This attitude is possibly an example of reversion, and is seen in the statues of ancient Egypt.

He therefore calls it the "Ancient Egyptian attitude."

Finally, as we go about our daily duties, we all recognize the dementia præcox "make-up" as a practical clinical entity, which fact of itself is suggestive of a basis of biologic significance.

The view, based on results of the Abderhalden dialysis method, that the disease is an "endocrinopathy" depends on evidences of various morbid proteins in the content of the blood serum.

The view of Orton[16] on this subject may be here presented as that of a competent critic—

> Even if we accept the theory and the results of its most hopeful investigators, we are only brought to the beginning of a wide field of investigation; as by the interpretation of the theory, the results speak only for a faulty metabolism in specific organs and as yet give no light on the underlying causes, *i. e.*, the fact that the metabolism of the testicle and brain are disturbed gives no insight into the *cause* of such disturbance.

To the present writer it would seem quite conceivable that the indications of wide-spread defects in various organs and their premature degeneration—even if established, are also logically attributable to general deficiencies of "make-up" and consequent undue susceptibility to infectious or other disease agencies. In other words, they may argue in favor of a biologic or basic defect.

To sum up:

(1) In the interpretation of the rôle of the biologic factors in this psychosis, so far as the evidence available at present permits, we must recognize the fact that, in the subject of dementia præcox, we have to deal with one of the "by-products" of the "Laboratory of Nature," an organism inadequate to adjust itself to its normal environment, owing to an arrest of evolution and a premature and irregular involution. Such an organism may be likened to a "proper soil." *Not every youth therefore can develop a dementia præcox form* of break-down of the psychic mechanism.

(2) The clinical course of the disease, and the findings of Southard,[7] suggest destructive agencies, which may influence the rate and amount of "deterioration." Here the *"specific disease"* element must be considered as a possibility. Such element may be viewed as playing the rôle of a noxious

weed, or destructive parasite, damaging the immature mental "crop" already started.

(3) Psychogenic factors (situations, conflicts, etc.) may quite plausibly be likened to "the seed," determining the character of the subsequent "abnormal crop," *i. e.*, the "form and content" of the psychosis, its "trends" and other psychic activities.

CONCLUSIONS.

The mere presentation of evidence of the nature of a disease is obviously of little practical value in itself. To be fruitful in results it should point the way to *constructive lines of thought*. What useful lesson may we learn from a study of these various *biologic aspects* of dementia præcox?

Since "mind" in its complete expression, includes the end results of *all reactions* of the animal organism to its environment, it is obviously impossible to draw a sharp scientific line of demarkation between psychology and psychiatry. The phenomena of the two sciences may be said to represent merely differing results of "rustling of the leaves" on the higher branches of the "tree of biology." Our distinctions therefore are often arbitrary, based on the *expediency* of social conduct. Hence they may vary in different races and in the same race at different stages of development. The same truth applies to individuals.

Any practical plan of therapy for dementia præcox should recognize the biologic tripod of *sub-evolution, neuro-toxæmia*, and faulty *psycho-genesis* as the probable basis of the disease. Our efforts therefore should be directed toward improving the "soil," removal of "weeds" and changing the "crop." The obvious indications are, (a) removal of the patient from sources of "psychic-conflicts" and "difficult adjustments" at as early a stage as possible. This means, of course, in practically every case, removal from home and home influences; (b) *rest*, physical and mental, *in bed*, during the acute stage, so that the physiological energies may be conserved and resistance to the toxic element may be promoted; (c) attention to anemia and other morbid blood states—if a leucocytosis could be induced it would probably be desirable in some cases; (d) eliminative measures by hydrotherapy and otherwise are very important; (e) nutritional and constructive agencies must be pushed to the limit.

As general health and well-being improve under this course, moderate exercise in the open air and suitable occupational and diversional therapy become useful.

The difficulties of productive psycho-analysis and psycho-therapy are obviously great, in the fully developed psychosis, but their possibilities in very early stages of the disease may be correspondingly great.

Under the above outlined methods of management, some cases improve so as to be able to resume family and social life to some extent; others rank in statistics as "recovered," though it is probable that they would be more correctly labelled "recovery *with defect.*" It is conceivable, however, that in exceptionally favorable subjects, in an early stage of the illness, under the

modes of management just outlined, the neuro-toxic element of the disease may "run its course," leaving a minimum of deterioration; and that the dynamic impulses of a beneficent nature, latent for a time, now relieved of their handicap, may reassert their powers. Evolution may then go on to a fairly normal completion —*for that individual.* These are the cases that may be said to really "recover." They are rare, but they encourage us to try and to hope.

REFERENCES

1. King, Captain Edgar, M. C., U. S. A.: Mental Disease and Defect in United States Troops. War Dept., Office of The Surgeon General, Bulletin No 5, March, 1914.

2. N. Y. Times: Editorial, May 17, 1916.

3. Peterson, Frederick, N. Y.: Personal communication February 4, 1916.

4. *Ibid.*: February 12, 1916

5. Lilienstein, S., Bad Nauheim, Germany: Personal communication, March 6, 1916

6. Kraepelin: Psychiatrie, 1913.

7. Southard, E. E.: On the Topographical Distribution of Cortex Lesions and Anomalies in Dementia Præcox, with Some Account of their Functional Significance. Amer. Jour. Insanity, LXXI, 383, 603, October, 1914-January, 1915.

8. Meyer, Adolf: The Dynamic Interpretation of Dementia Præcox. Amer. Jour. of Psychology, XXI, July, 1910, 385-403.

9. Hoch, August: Constitutional Factors in the Dementia Præcox Group. Rev. Neur. & Psych., VIII, August, 1910, 463.

10. Quoted by Hoch: Review of Bleuler's Schizophrenia. Rev. of Neur. & Psych., X, June, 1912, 259

11. Campbell, C. Macfie: A Modern Conception of Dementia Præcox. Rev. of Neur. & Psych., VII, October, 1909, 623.

12. Kraepelin, Emil: Lectures on Clinical Psychiatry English translation by T. Johnstone. N. Y., Wm. Wood & Co., 1904, 24.

13. Kraepelin, E.: Psychiatrie, 8th ed., 1913

14. Stoddart, W. H. B.: Mind and its Disorders, London, 1908, 230, 231 Same 2nd ed., 338 339, illust., 1912.

15. Steen, R. H.: A Characteristic Attitude, etc. Jour. Ment. Sci., January, 1916, p. 179. (Quoted from Rev. Neur. & Psych., March, 1916, p. 132.)

16. Orton, Samuel T.: The Present Status of the Application of the Abderhalden Dialysis Method to Psychiatry. Amer. Jour. Insanity, LXXXI, January, 1915, 589.

In addition to the original sources recognized in the above list grateful acknowledgments are due to my friend Dr. William Ravine for notes and translations of the German; to my associates Drs. B. A. Williams and Emerson A North for clinical and statistical data and some of the illustrations; to Dr. F. W. Harmon, of Longview State Hospital, Cincinnati, for the courtesies of access to the wealth of material contained in that institution, and to Dr. H. Douglas Singer for valued suggestions and references.

PERNICIOUS ANEMIA WITH MENTAL SYMPTOMS

OBSERVATIONS ON THE VARYING EXTENT AND PROBABLE DURATION OF CENTRAL NERVOUS SYSTEM LESIONS IN FOUR NECROPSIED CASES.*

Louis A. Lurie, M.A., M.D.

Cincinnati

Our knowledge of pernicious anemia is being constantly enriched, especially our knowledge relating to the changes occurring in the nervous system. And justly so, because after all, next to the blood changes, the most characteristic and frequent clinical findings are on the part of the central nervous system. Minnich† (1893) demonstrated lesions in the spinal cord in approximately 70 per cent. of cases of pernicious anemia. Of forty-one cases treated by Billings (1900), forty showed neurological symptoms. In a very recent (1919) report of the 150 moderately advanced cases of pernicious anemia examined at the Mayo Clinic, Woltman found indisputable evidence of nervous tissue disintegration in over 80 per cent.

Formerly the neuropathology of this disease consisted chiefly in descriptions of the changes taking place in the spinal cord. It has been but comparatively recently that investigation has shown that these changes are not limited to the cord, but involve other parts of the central nervous system as well. (Pfeiffer, Barrett, Woltman.)

ETIOLOGIC FACTORS.

In discussing the etiologic relationship between the brain and cord changes on the one hand and the blood changes on the other, one is confronted by various theories, each of which has its ardent supporters. The reason for this diversity of opinion is our ignorance of the fundamental cause or causes underlying this disease. Practically all are agreed that the clinical syndrome which we call pernicious anemia is produced by one toxin, the nature and origin of which, however, are still mooted points.

We feel safe in assuming that the disease is due to a toxin because of experimental work performed along similar lines in cases of anemia due to the *Bothriocephalus latus*. It was long known that all individuals harboring these parasites did not develop pernicious anemia. Of those that did develop it nothing was disclosed either during life or at necropsy to show that they possessed any characteristics that might be regarded as predisposing them to this disease. The natural inference, then, was that the parasite was the variable factor. In other words, some change occurred which transformed the parasite from a harmless, though unwelcome, inhabitant of the intestinal tract into a deadly menace.

Elaborating on this idea, Shapiro advanced the theory that when the worm died or became diseased, noxious substances were produced which on being absorbed produced the anemia. The work of Wiltschur strongly supports this view. He examined twelve worms, the removal of which cured severe anemias and found that in "all cases the worms were either dead, decomposed, or sick."

Reasoning by analogy, we feel confident that the Addison-Biermer type of anemia is also due to a toxin. As to its origin, we as yet know nothing very definite. Much work has been done in this connection. The regularity with which changes occur in the gastro-intestinal tract, has led many to believe that this condition is essentially a disease of the gastro-intestinal tract (Grawitz-W. Hunter). Atrophy of the gastric mucosa, achylia gastrica, and intestinal stasis are frequently encountered. Berger and Tsuchiya found that extracts of the gastric and intestinal mucous membrances from patients dead of this anemia were more hemolytic than extracts of normal mucous membranes. This statement, however, is disputed by Ewald and Freidberger.

It is well known that certain chemical substances, such as oleic acid, saponin, phenylhydrazin, b-amino-azolyl-ethylbenzaldehyd and p-oxyphenylethylamin are capable of producing intense hemolysis. One of these substances, namely p-oxyphenylethylamin, has been isolated by Iwao from autolyzing pancreas, putrefying horse flesh and from Swiss cheese. Conceivably this compound may arise in the intestinal tract as the result of decomposition of food. Berthelot and Bertrand have shown that among the flora of the intestinal tract there is a bacillus, the *B. aminophilus*—which is capable of producing p-oxyphenylethylamin from tyrosin. Thus we can readily see how intestinal stasis could be a great factor in the production of pernicious anemia.

On the other hand, others have taken the stand that the increased production of hemolysins is due to a condition of hypersplenism. The toxin is carried by the blood to the spleen where certain changes occur. According to Moffit, "erythrolysis does not take place in the spleen but in some way the erythrocytes are sensitized and prepared for later destruction in the liver, marrow or lymph glands." From this viewpoint it would be easy to account for the beneficial results that often follow splenectomy.

Granting that a toxin is responsible for this condition the lack of the fundamental knowledge as to its origin and *modus operandi*, makes it all the more difficult in trying to solve the causal relationship between the blood and the central nervous system changes. We have a mass of clinical and histopathologic data that has been accumulating ever since Addison first described pernicious anemia in 1855. Investigators have naturally tried to correlate these facts, and in correlating them, have advanced many theories. Most of these theories have long since fallen by the wayside; others, however, have remained and can be briefly summarized as follows:

1. A toxin produces the anemia which in turn produces another toxin that causes the changes in the brain and spinal cord.

2. The anemia itself acts as a toxin which through malnutrition causes the changes observed in the central nervous system.

3. The toxin acts independently on the blood and on the central nervous system.

Before discussing the relative merits of these theories it is essential to bear in mind certain well established facts. The absolute lack of correspondence between the brain and cord changes on the one hand and the anemia on the other hand both from anatomic and clinical standpoints has long been known.

Clinically there are many cases in which the neurological symptoms appear before the anemia. In other cases, both conditions arise simultaneously, and in still other cases, the anemia is present long before the appearance of any neurological disturbances.

Similarly, either condition may improve without a corresponding improvement in the other, or both may show a co-ordinate improvement.

Furthermore, it has been stated (Goebel) that cases that clinically show disturbances of the central nervous system may on section show no demonstrable organic changes.

From the above statements, it is obvious that the first two theories are untenable. So long as it is possible for the nervous symptoms to precede the appearance of the anemia, then it is impossible to maintain that the anemia either directly or indirectly, that is, through the production of another toxin, produces the cord and brain changes.

The third theory, however, overcomes this objection. If we assume that the toxin acts independently on the central nervous system and on the blood, then we can say that in one instance, the toxin acts first on the central nervous system and then on the blood, thus producing those cases in which the disease is ushered in by the nervous symptoms. In another instance, it acts on the blood first. These are the cases in which the anemia precedes the development of neurological symptoms. In still another instance, the toxin acts simultaneously on the central nervous system and on the blood, thereby giving rise to a clinical picture showing both brain and blood changes at once. (Nonne-Billings.)

So far so good. But, on the basis of this theory, how can we explain the fact that in cases where similar therapeutic measures, for example, splenectomy, have been instituted, some will show an improvement in the neurological symptoms without any improvement in the blood picture, while others, reversely, will show a betterment in the anemia without a corresponding betterment in the cord and brain changes.

Decastello[1] performed a splenectomy on a patient who had suffered from the disease for less than a year. The anemia was severe and the spleen but slightly enlarged. Since the operation, the patient has shown marked improvement clinically but with no alteration in the blood picture.

Harpole,[1] on the other hand, performed a splenectomy on a patient who

[1] See Pearce, Krumbhaar and Frazier: The Spleen and Anemia.

Page 288

had been known to have had the disease for at least two years. The anemia was moderately severe. Following the operation there was an immediate improvement. The patient has continued in fair health with only a slight anemia but with *persistence of the spinal cord symptoms.*

Furthermore, how will this theory account for those cases which showed clinical evidence of involvement of the central nervous system, but in which the pathologist, on necropsy, is unable to discover any demonstrable lesion?

It seems to me that if we judiciously combine the second and third theories into some such theory as the following, we shall have one that will account for all of the various manifestations of pernicious anemia. Briefly stated it would read as follows:

1. One toxin produces pernicious anemia.

2. This toxin acts independently on the blood and on the central nervous system.

3. The anemia itself, after it has persisted for a considerable length of time, interferes with the metabolism of the nerve cells, thereby indirectly enhancing the poisonous action of the toxin so that instead of being merely an irritant to the nervous tissue, it becomes a highly destructive agent. In this way, the changes which at first were purely temporary and functional now become permanent and organic.

In other words, I think that we can with justice assume that the nervous structure is open to two lines of attack, namely, (1) a direct or frontal attack by the toxin, and (2) an indirect or flank attack by the anemia. If the anemia is improved before the latter attack has materalized we get an improvement in the neurological symptoms and such a patient on necropsy will show no pathologic cord or brain lesions.

If, however, the anemia has persisted long enough for both frontal and flank attacks to materialize, then improvement in the blood picture will not be followed by a corresponding improvement on the part of the central nervous system. Such cases coming to necropsy will show the changes that are usually found in the cords and brains of pernicious anemia patients.

This theory is in line with the views of Bonhoeffer, who thinks that the psychoses that some patients present are not due to the direct action of the toxin but to the interposition of some metabolic changes in the nerve cells.

Christian's recent work strengthens this view also. He tested the renal function in fourteen cases of pernicious anemia and found that the latter produced a chronic nephritis which could be improved by improvement of the anemia, provided the latter had not persisted for too great a length of time. His conclusions are:

In patients with pernicious anemia the disease is accompanied by a disturbance of renal function, as measured by renal dietary tests, which is similar to that found in patients with advanced chronic nephritis. In these patients there is no other evidence of chronic nephritis and the disturbance appears to be due to the anemia, decreasing with the subsidence of the severity of the anemia *unless the anemia is maintained so long that a permanent disturbance of renal function ensues.* [Italics mine.]

This theory stated in its entirety would read as follows:

1. One toxin causes both the blood and the central nervous system changes.

2. This toxin acts independently on the blood and on the central nervous system. This would account for those cases in which (a) the neurological symptoms manifest themselves before the anemia, or (b) in which the anemia precedes the brain and cord changes, or (c) in which both conditions arise simultaneously.

3. As soon as the typical blood picture of pernicious anemia develops and persists for a considerable length of time, the metabolism of the nerve cells is so impaired that the changes which were purely functional at first and due to the irritating action of the toxin alone, now become organic and permanent. Hence, no matter how greatly the physical state is improved, be it through splenectomy, transfusions, or drugs, no improvement on the part of the nervous system follows. The damage is irreparable. If, however, the hemolysis has not lasted very long, then improvement in the neurological symptoms may be expected to follow the exhibition of proper therapeutic measures. We can thus account for the apparent contradictory results in the cases reported by Decastello and Harpole. In the latter case, the anemia had lasted for at least two years. Removal of the spleen was followed by an improvement in the blood picture but with no improvement on the part of the central nervous system. Here we can rightly assume that the anemia had interfered to such an extent with the metabolism of the nervous elements that permanent lesions had been produced.

In the former case, the anemia had existed for a much shorter period and therefore splenectomy was followed by improvement in the neurological symptoms.

In line with this theory is the fact brought out by Pearce, Krumbhaar and Frazier and their co-workers, that if splenectomy is performed before the blood has reached an extreme degree of deterioration, not only is the operative risk lessened but the improvement is greater and more lasting.

Finally, on the basis of this theory it is easy to account for those cases which during life showed clinical evidence of involvement of the central nervous system but which on necropsy showed no lesion, either in the cord or brain. In these cases, the irritant action of the toxin had not been aided by the anemia.

MENTAL SYMPTOMS OF PERNICIOUS ANEMIA.

Many observers have called attention to the mental symptoms that frequently occur in pernicious anemia patients. The early investigators simply noted the somnolence, apathy, and coma that usually preceded the fatal termination of the disease. Later, however, it was noted that the mental symptoms were not simply terminal but that in a great many cases they constituted a dominant part in the clinical picture. Marcus and Langdon have each reported cases in which the mental changes appeared before the

anemia or, at least, before the blood picture was sufficiently developed to warrant the diagnosis of pernicious anemia. Langdon termed these cases "prepernicious anemia." The psychic disturbances may range from mild depression to violent maniacal outbursts. Some cases will show irritability, hyperkinesis, delusions and hallucinations. Other cases will show indifference, apathy, and severe melancholia. Whenever a distinct psychosis, such as manic-depressive insanity, is present, the majority of observers look on it as separate and distinct from the pernicious anemia. At most, in such cases the pernicious anemia may be regarded as a predisposing factor. At present it is generally accepted that the psychotic manifestations should be classified with the exhaustion and toxic-infectious psychoses. Barrett expressed it very clearly when he said:

> As to the clinical position, it would seem that they must be placed among the paranoid conditions which are symptomatic of a toxic organic process affecting the central nervous system—analogous to the paranoid conditions which have been noted in tabes, alcoholism and from certain drugs.

It has been but comparatively recently, however, that efforts have been made to link up the mental disturbances with the cortical changes. Barrett found many pathologic changes in the cortex, but as a whole not of the specific type. They appeared to be rather similar to those changes which occur in conditions of chronic intoxication, due, for example, to chronic alcoholism. The blood vessels showed the most constant changes. There were in the nature of swelling of the intimal cells and in some active proliferative changes. The most important findings, however, are the focal lesions, which correspond very closely to the lesions so characteristically present in the cord.

Weltman made a very thorough and exhaustive study of seven cases. His findings led him to the conclusion that the brain and cord changes run fairly parallel and with about the same frequency; and, furthermore, that patients who show degenerative changes in the spinal cord at necropsy, usually show the same type of lesion in the brain also. In the medullary substance of sections of different levels of the brain, he also found areas of degeneration of the Lichtheim type that are identical with those that are usually found in the posterior and lateral columns of the spinal cord. In addition to these focal areas of degeneration he noticed diffuse areas of degeneration in the long association tracts and in the short commissural fibers that pass from one gyrus to another. He calls attention to the fact that the gray matter shows involvement of a focal nature also, the cells of the marginal gray layer being principally involved.

REPORT OF CASES.

Technic.—The following report is based on the study of four cases. In each case the brain and spinal cord had been fixed in formaldehyd solution and cut in the frontal plane. Blocks of tissue about 5 mm. in thickness were taken from each of the following regions: (1) left motor area; (2) middle of pons; (3) middle of medulla; (4) cervical region of cord; (5) dorsal region of cord; (6) lumbar region of cord In addition, sections were also taken in some cases from the right motor area, the left internal capsule, and the peduncles. These were selected because, macroscopically they

seemed to offer promising material for study. These blocks were then mordanted, embedded in parlodion, cut, under alcohol, into sections 25 microns in thickness and stained by the Weigert method. Those stained with cresylecht-violet, had formalin fixation and paraffin embedding and were cut into sections 6 microns in thickness. Some of the sections were also stained with hematoxylin and eosin.

Case 1 (Necropsy 15-106). *History.*—O. D., a white man, aged 75, was admitted to the psychopathic department, Boston State Hospital, September 27, 1915. He was mentally confused and had hallucinations and delusions of various kinds.

Family History.—The family history is entirely negative. There is no history of nervous or mental diseases in any of the collaterals.

Personal History.—The patient was born in Germany and had the ordinary diseases of childhood. He had a severe attack of rheumatism sometime between the ages of 50 and 60 years. About four or five years ago he began to have bladder difficulties. He left school at the age of 15 and spent the next twenty-six years at sea. He then came to this country and worked steadily for a ship concern until the onset of the present illness, which prevented him from performing his duties properly. His daughter stated that he left his work because his mind gave out and because he had dizzy spells and would fall on the street. His condition gradually became worse and he had begun to dislike people, preferred to stay alone, was irritable and ugly. He was always com-
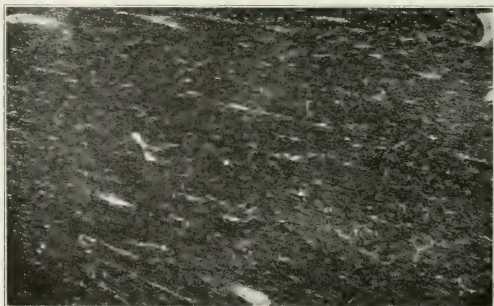
Fig. 1 (Case 1). Section of left motor area, showing areas of degeneration in close proximity to the blood vessels. One, in the upper right hand corner, is at the point of bifurcation of a capillary. In the upper left hand corner a focus of degeneration is seen surrounding blood vessels. Weigert's myelin sheath stain. Magnified about 40 diameters.

plaining and found fault with everything. He had delusions of persecution. His daughter had become afraid of him because of his ugliness. For the past three years he had been very pale and complained of numbness of the feet. However, he did not drag his feet.

Ten weeks before admission, the patient fainted and afterward had a chill, a period of vomiting and later, fever which reached 102 F., after which he had a peculiar cold period. It seems that the mental confusion, hallucinations, rambling and incoherent talk have chiefly developed since the onset of this attack of chill, vomiting and fever. Previously he had always been constipated but during this bed-ridden period there was diarrhea and he had no control of rectum or bladder.

His hallucinations varied. At one time he saw a man in the room with him, sitting with his hat on; at another time, he saw trucks and a steamer in his room. At times he feared that he was going to be put down into the cellar, and at other times he thought he was being kept there. He also had periods of memory defect.

Examination.—On examination, the face was seen to be puffy and pasty and the skin unduly pale. There was a sytolic murmur at the apex which was feebly trans-
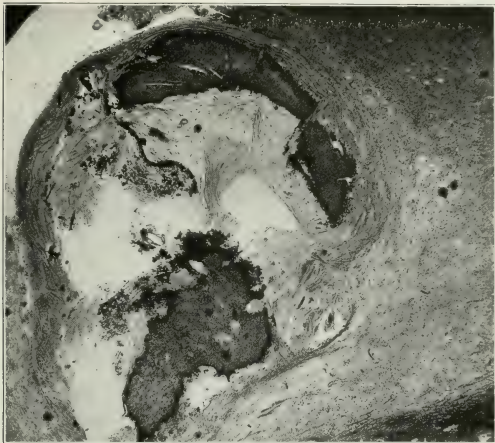
Fig. 2 (Case 1). A large area of softening in the cortex produced by rupture of a large blood vessel. Weigert's myelin sheath stain.
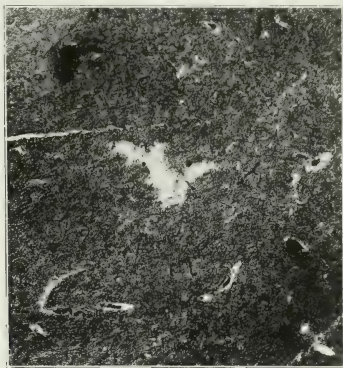
Fig. 3 (Case 1). A so-called Lichtheim plaque in the left internal capsule. Weigert's myelin sheath stain.

mitted to the axilla. The aortic second sound equaled the pulmonic second sound. The pulse was regular and of good volume. The blood pressure was: systolic, 130; diastolic, 70. The breath sounds were faint and crepitant; râles were heard all over the back and front. The liver was enlarged but not tender. The spleen was not palpable.

Neurologic examination showed normal reacting pupils. The fundi could not be examined on account of the patient's restlessness. The triceps and biceps were present and equal on both sides. The abdominal reflexes were only obtained in the left inguinal region. Both knee jerks were absent. The same was true of the Achilles reflex.

Fig. 4 (Case 1). Here the miliary foci described by Preobrajensky are very conspicuous. The contrast between them and the larger so-called Lichtheim foci, three of which are also shown in this picture, is very striking. The foci of Preobrajensky are much smaller, more numerous and more sharply defined than the Lichtheim plaques. Although not shown in this photograph, in a good many cases an undamaged nerve fibril may be seen traversing a small focus. Weigert's myelin sheath stain of pons.

There were no Babinski, Gordon or Oppenheim reflexes. There was no ankle clonus. The deep sensibilities were not tested because the patient could not co-operate.

The urine showed a slight trace of albumin and an occasional red blood corpuscle, and a few granular casts and a rare hyaline cast. The blood Wassermann reaction was negative. Examination of the spinal fluid showed the following: Fluid, clear; albumin, + + +; globulin, + +; cells, 4; small lymphocytes, 100 per cent. Colloidal gold chlorid test, 0 0 0 0 0 0 0 0 0 0. Blood Examination: This revealed the following: Hemoglobin, 30 per cent. (Sahli) with a color index of 1.66; red blood cells, 2,528,000; white blood cells, 4600. A differential count (100 cells) gave polymorphonu-

clear leukocytes, 71 per cent.; small lymphocytes, 16 per cent.; large lymphocytes, 10 per cent.; eosinophils, 3 per cent.

There is a great variation in the size of the red blood cells with a large percentage of macrocytes. Poikilocytosis is marked. No achromia.

Course.—September 28: Patient had been lying quietly all day in a semi-comatose condition. He does not comprehend questions, rarely speaks, and when he does, cannot answer questions relevantly. His mind wanders deliriously, calling for "Annie" and telling fabulous tales.

September 30: Condition the same. The skin is very pale and has a slight lemon yellow tint. Both knee jerks and Achilles are absent. All the toes were drawn up on stroking the sole of the foot and in testing for Oppenheim's sign.

October 1: The patient has continued in the same low grade semiconscious semi-delirious condition previously noted. He continues to call deliriously for "Annie," but
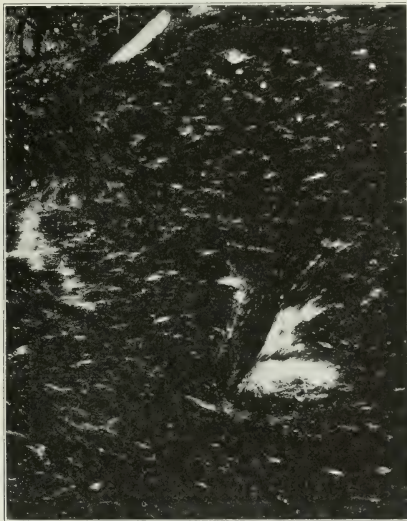
Fig 5 (Case 1). Another view of a different section of the pons. The relationship of the large plaques of degeneration to the blood vessels is very clearly shown. Here we see again the formation of an area of degeneration at the bifurcation of a capillary. A large number of the smaller foci are also present. (Weigert method.)

otherwise makes practically no intelligent remarks, occasionally rambling about "the boat." The yellowish tint of the skin is more marked. Moist, bubbling râles could be heard all over the chest. Patient failed rapidly and died early in the afternoon.

Necropsy.—This was performed six hours after death. The body is that of a well built and nourished, white man, 176 cm. in length. The skin is waxy gray with a slight yellowish cast. There is a faint edema of the lower legs and some atrophy of the left thigh. The pupils measure 5 mm. in diameter and are equal. There is a superficial decubitus over the sacrum. Rigor mortis is faintly present.

Ventral Section: The fat is lemon yellow in color and measures 2 cm. over abdomen and 1 cm. over thorax. The spleen is adherent to the external lateral surface. The appendix above the pelvic brim measures 7 cm. in length. The bladder is distended and the intestines somewhat injected. The diaphragm arches to the fourth rib on the right side and to the fifth interspace on the left side. The gall-bladder is distended and contains many stones.

Thorax: The bone marrow is yellowish pink in the sternum. There is no free fluid in either pleural cavity, but there are adhesions at the apex of the right lung. The pericardium is heavily loaded with fat. The apex of the heart is in the fifth interspace.

Heart: Weight, 453 gm. The epicardial fat is fairly abundant. The descending branch of the left coronary shows sclerosis. The right coronary and circumflex arteries show constrictions with calcifications. Every valve is thickened, particularly the aortic which shows distortion of the cusps. There are some vegetations which are calcified around the origin of the left coronary in the internal surface of the aorta.

Figs. 6, 7, 8 (Case 1.) Sections of the cervical, dorsal and lumbar regions of the spinal cord. The degeneration of the posterior columns is marked. This degeneration is only moderately severe in the lumbar region, but becomes progressively worse in the upper portions of the cord. It reaches its climax in the cervical region. Here, the destruction is seen to be very severe. Within the area of degeneration, large, jagged holes are present. This is in marked contrast to tabes dorsalis. In the latter condition, the degeneration of the posterior columns, as a rule, is greater in the lumbar region than in the cervical region. The degeneration in the lateral columns, which as a whole is much less than in the posterior columns, increases in intensity from above downward. The posterior roots in the lumbar section show evidences of degeneration. The hole seen in the lateral column of each section has been made to mark the right side of the cord. This applies to all the following photographs of the cord. Weigert's myelin sheath stain (× 10).

The myocardium is pinkish gray in color and contains multiple white streaks measuring from 0.5 to 0.6 cm. in extent.

Lungs: Weight—left lung, 385 gm.; right, 1200 gm. The right lung pits on pressure, but is crepitant for the most part. There is a slight thickening of the pleura at the apex. The bronchi are reddened and show frothy fluid adherent to mucus.

The left lung has a collapsed area in the lowest part of the upper lobe and in the posterior part of the lower lobe. Section of this shows it to be somewhat redder but not wetter than usual. The bronchi are reddened but the peribronchial lymph nodes are not enlarged.

Spleen: Weight, 165 gm. There are two fetal lobulations on the lower border. The capsule is somewhat thickened and wrinkled. The pulp is red and watery, and retracts on section. The trabeculae are increased and the malpighian bodies are numerous.

Adrenals: They are embedded in fat and are large. On section they show marked mottling of cortex and medulla with yellow and red. The medulla is scarcely to be differentiated from the cortex.

Figure 7

Figure 8

Kidneys: These are deeply embedded in fat. The capsule strips with difficulty.

Liver: Weight, 1800 gm., and has a yellowish pink color. The capsule is slightly thickened and there is a focal area of adhesion to the diaphragm. Section shows a fairly pale homogeneous substance. The gall-bladder contains forty-eight stones.

Pancreas: The splenic artery is tortuous, markedly sclerosed and calcified. Every level of the pancreas examined shows fat replacement in varying amounts.

Gastro-Intestinal Tract: Section of stomach shows the wall somewhat thickened and glossy. No rugae are present. Yellow mucus drips from the surface. There is nothing of note in the intestinal tract.

Special Examination: The bone marrow of the left femur was inspected, and found to be raspberry red in color.

Brain: The dura is very adherent, but not particularly thickened. The superior surface of the brain generally is firmer than normal. The convolutional pattern is rich. The pia mater is not thickened except slightly in the sulci over the vertex.

Base of brain shows a small aneurysm in the middle part of the left posterior communicating artery. The fourth ventricle shows clear granulations. The brain weight is 1100 gm., which, according to Tigges' formula, shows a loss of 308 gm. The cord shows minute specks of translucency in the middle of the posterior columns.

COLLOIDAL GOLD CHLORID REACTION.

	1	2	3	4	5	6	7	8	9	10	
Cortex	1	2	2	2	2	1	1	0	0		Bloody
Right base	1	2	1	1	1	0	0	0	0		Bloody
Left base	3	2	2	2	1	1	0	0	0		Bloody
Third ventricle*	0	0	0	0	0	0	0	0	0	0	
Spinal fluid	0	0	0	0	0	0	0	0	0	0	
Pericardial fluid	0	0	0	0	1	1	1	2	2	3	

Histologic Examinations.—Weigert Sections—Left Motor Area: Macroscopically, one sees a cross-section of a very large blood vessel with thickened walls. Surrounding it, in the medullary substance, is a very large area of softening which shades off gradually into the surrounding normal tissue. On microscopic examination, this area of softening is seen to be composed of destroyed nerve fibers, with here and there small patches of neuroglia and intact nerve fibers. The entire part appears cribriform owing to the presence of many large vacuoles, some of which have apparently run together to form large cavity-like spaces. In the medullary portion, the blood vessels are thickened, the perivascular spaces are dilated and in a great many instances there is a thinning out of the myelin sheaths in their immediate neighborhood. In many cases, this destructive action has gone on to complete degeneration so that irregularly circumscribed areas which vary in size and structure have been formed. Some are filled with debris and crossed by a few undegenerated nerve fibers, while others are clear and hyaline-like in appearance. At the bifurcation of one of the capillaries there is a so-called Lichtheim focus. In the cortical area the blood vessels are numerous and have very thick walls. Some are seen to be ruptured. The perivascular spaces are greatly distended.

Internal Capsule: Here there are also vascular changes both in the gray and white matter. Many plaques of different sizes and shapes are seen surrounding the blood vessels. The perivascular spaces are uniformly distended. In a small portion of the medullary substance one can see a few of the miliary foci described by Preobrajensky.

Pons: The most striking feature in this section are the miliary foci of Preobrajensky. They are very numerous and confined entirely to the medullary portions and are most numerous in the center. Practically all are of uniform shape but not of uniform size, some being three times as large as others. The smallest are about the size of small lymphocytes. They are fairly definitely circumscribed and have a punched out appearance. In many, an undamaged nerve fibril may be seen passing through the destroyed area. In addition to these miliary foci of Preobrajensky there are quite a number of well defined Lichtheim plaques. These bear a close relationship to the blood vessels.

Cord: With the unaided eye one can see a distinct circumscribed degeneration of the column of Goll. In the cervical region, this has proceeded to apparent cavity formation. The degeneration, although still sharply defined in the thoracic region, becomes less and less marked as we pass to the lumbar region. The reverse, however, is true of the lateral columns. Here the degeneration, which is much slighter than in the posterior columns, increases from above downward. On microscopic examination, we see that the column of Goll is practically entirely destroyed. Several large spaces with irregular jagged edges are conspicuous. Smaller vacuoles are numerous. Here and there are evidences of small hemorrhages. The blood vessels are intensely congested.

Cresylecht-Violet Sections—Left Motor Area: The pyramidal cells appear shrunken and granular. Many of the pericellular spaces are filled with a large num-

her of satellite cells. The perivascular spaces, especially those of the cortical area, are distended.

Internal Capsule: Here and there are small islands of sclerotic tissue, apparently not related to the blood vessels. The pyramidal cells are uniformly shrunken, irregular in outline, and in a great many, the nucleus is displaced. Some satellitosis is present. From one pericellular space, the nerve cell had entirely disappeared and its place is occupied by five satellite cells.

Pons: Small, clear, oval areas corresponding in size and position to the miliary foci of Preobrajensky, seen in the Weigert section of the pons, are also present here. In the gray matter there are many small patchy areas of degeneration. The nerve cells are not as noticeably abnormal as those of the preceding sections.

Medulla: Pigmentation of the nerve cells is marked. The perivascular spaces are tremendously distended and filled with debris. Large areas of degeneration are present in the white matter. The pyramidal tracts are full of vacuoles. Two types of glia cells, differing principally in size, were observed. The larger ones, in all probability, simply represent more mature forms. They are profusely distributed over the entire section, but more particularly in the region of the olivary nuclei.

Cord: The posterior columns contain numerous thin walled capillaries which are surrounded by large amounts of glia cells and fibers. The glia replacement cells are of comparatively large size and of the stellate type. An occasional undegenerated or only partially degenerated nerve fiber is seen. The increase in the number of blood vessels is most noticeable in the dorsal portion of the cord. The nerve cells show various changes. Some are very much shrunken and irregular in outline; others contain numerous variously-sized granules; still others are swollen and contain a large amount of yellow pigment. Pigmentation is present both in the anterior and posterior horn cells, but occurs more frequently and uniformly in the former. This pigmentation differs from that normally found in the cells of persons of advanced years, in that it is diffuse, somewhat granular and not clumped at one pole of the cell body. In these cells, the pigment is centrally located and apparently has pushed the protoplasmic substance to the extreme periphery of the cell. In some of the cells, the nucleus is displaced to one side and stains poorly.

Case 2 (Necropsy 16-59). *History.*—C. C., a white woman, aged 54. Was committed to the Boston State Hospital, April 25, 1916, with the diagnoses of pernicious anemia and symptomatic psychosis.

Family History.—Her mother died at the age of fifty of tuberculosis. Of six siblings, two have died of tuberculosis; one is now in a hospital suffering from tubercular trouble; one (a sister) is excessively alcoholic and has seizures with unconsciousness, and one died in infancy.

Personal History.—The patient was born at Salem, Mass., in 1862. Her education was limited but she was able to read and write. She drank a little beer and smoked cigarets for about a year. She formerly used snuff. Her sexual habits, as far as could be ascertained, were normal. She was never very cheerful, and many times greatly depressed. She was somewhat obstinate, but in many ways showed that she could be very sympathetic and kind. She was known to be hypochondriacal and apprehensive. She was a good housekeeper, was sociable and made friends. Her first marriage occurred when she was eighteen years old. By that husband she had one child, who died at the age of three of "water on the brain." At the age of thirty-six she was again married, but by this marriage she had no children and no miscarriages. Since the second marriage she has led a very lonesome life.

Medical History.—In childhood she was at the Salem Hospital because of anemia. According to the statements of her acquaintances, she has always been pale. She always claimed that she was a spiritualist and "could see dead people." Early in 1915 she went to the Eye and Ear Infirmary because she thought that she had cancer of the throat. In May of that year she was for nearly three weeks a patient at the Massachusetts General Hospital with what was diagnosed as pernicious anemia. At that time she was irrational and had visual hallucinations. She saw animals and would point her fingers at imaginary objects. She walked unsteadily and fell frequently but never lost consciousness. Sometimes she had complete loss of vision for a few minutes. Until a year previous to this attack, the patient was able to do her housework. Six weeks ago she became much worse; very excitable, swore and used obscene language. Recently she carried on an imaginary conversation with her deceased daughter. She has also turned against her niece and niece's little girl of whom she has been very fond. On occasions she would "jump out of bed at people." There were no homicidal or suicidal tendencies.

Physical Examination.—The patient was a well developed and well nourished woman of fifty-four. Her face was of a striking pallor with a lemon yellow tinge.

The mucosæ were very pale. There was a harsh systolic murmur at the apex that was transmitted upward to the axilla. The liver was enlarged but not tender. The spleen was palpable in the left hypochondrium and the dullness extended to 3 cm. above the umbilical line. The blood pressure readings were: systolic, 105; diastolic, 45.

Neurologic Examination.—The pupils were equal and regular. They reacted well to accommodation but very sluggishly to light. There was no nystagmus or strabismus. The tongue protruded in the midline and appeared very anemic. The arm reflexes were all hyperactive. There was hyperesthesia of the lower extremeties. The knee jerks were equal but sluggish; the Achilles active and equal, and the plantars hyperactive. No Babinski, Gordon or Oppenheim reflexes were obtained. There was no ankle clonus.

A formal mental examination could not be made on account of her mental state. The patient appeared to be in a dazed, half asleep state. It was difficult to get her to comprehend questions, but when her attention was gained she usually answered the questions fairly well. When asked where she was born, she delayed before answer-
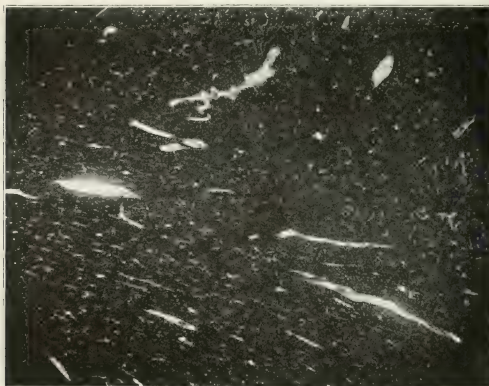
Fig. 9 (Case 2). Weigert's myelin sheath stain of left motor area showing small foci of degeneration and one larger area in intimate relationship with the neighboring blood vessels.

ing, then asked what the question was. She finally said that she was born in Salem. She did not know how long she had lived there. She answered questions as if very weary and gave the impression that the incorrect answers were due, in part, to lack of effort. She persisted in the feeling that her niece had intended to injure her and refused to see her. Her condition gradually grew worse and she was less and less easily aroused. Twelve days after her admission, she died.

Wassermann Reaction: Serum, negative.

Blood Examination: Hemoglobin less than 10 per cent. (Sahli); color index, 1.6; red blood cells, 780,000; white blood cells, 4,700; polymorphonuclear leukocytes, 60 per cent.; small lymphocytes, 32 per cent.; large lymphocytes, 8 per cent. The red blood cells showed marked anisocytosis and poikilocytosis, and some achromia. There was a large number of microcytes and macrocytes. No stipling or nucleated reds were seen.

A later blood examination showed hemoglobin less than 10 per cent. (Sahli); red blood cells, 550,000; white blood cells, 4,500; polymorphonuclear leukocytes, 61 per

cent.; small lymphocytes, 34 per cent.; large lymphocytes, 3 per cent.; transitionals, 0; eosinophils, 1 per cent.; mast cells, 1 per cent. Two normoblasts and one megaloblast were seen. The red blood cells showed marked variation in size and shape. There were very many small cells but the majority were macrocytes and the average volume index was increased. There was no achromia as the color index was high. Occasional cells showed marked polychromatophilia and occasional cells showed very marked stipling.

Necropsy Protocol.—The body is that of a well developed, poorly nourished woman, 157 cm. in length. Rigor mortis is not present. No superficial lymph nodes are palpable. The skin is lemon yellow in color. The necropsy was performed thirty-six hours after death. The pupils are equal and regular and 0.4 cm. in diameter.

Ventral Section: The abdominal fat is bright yellow; the thoracic and omental fat being bright lemon yellow. The liver is 12 cm. below the ensiform cartilage. The
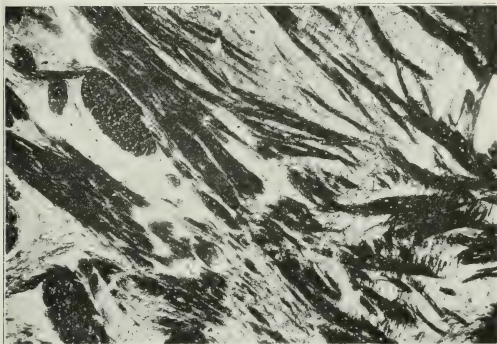
Fig. 10 (Case 2). A section of the pons stained by Weigert's myelin sheath method. Here again are very clearly shown the miliary foci of Preobrajensky in the medullary substance.

spleen is not encased in adhesions. The appendix is retrocecal and adherent to the cecum. The diaphragm arches to the lower border of the fourth rib on the right and to the lower border of the fifth rib on the left.

Heart: The myocardium of left ventricle shows tiger lily striations with here and there translucent areas. The muscle is soft.

Lungs: These are encased in adhesions. The cut surface is grayish brown in color at the apices. In the lower lobe it is pinkish-yellowish-gray. The connective tissue element is well marked. A frothy, grayish fellow, thick fluid is scraped from the cut surface.

Abdomen: The spleen weighs 185 gm. and is of firm consistency, with a shiny surface. It is purplish brown in color. The capsule is not thickened; the trabeculae are prominent and the malpighian bodies appear as pin points.

Kidneys: These showed cystic areas on the lateral edge. The capsules stripped easily.

Liver: This weighs 1,560 gm. It is shiny, mottled and of yellowish-brown color. The capsule in general is not thickened. It is of firm consistency.

Pancreas: Pale; otherwise there is nothing of note.

Gastro-Intestinal: The stomach is pale, glassy and atrophic in appearance near the cardiac end.

Head: The skull tables show a symmetrical thickening. There are slight patches of endostosis in the frontal region.

Superior Surface of Brain: There is no apparent atrophy and it is firm to the touch. There are inequalities between the first and second frontals and between the right and left prefrontals.

Base of Brain: The basilar artery is small and no sclerosis in the circle of Willis could be seen. There is a slight thickening of the pia around the third nerves, otherwise the cranial nerves show no abnormalities. The mammillary bodies are flattened. The brain is pale. The fourth ventricle is clear. A pressure ring cerebellum is noted. In the left base the fluid is yellow. This also applies to the cortex. However, neither the right base nor the third ventricle showed this condition. The spinal fluid was mixed with blood. The brain weighed 1,175 gm., which according to Tigges' formula gives a loss in weight of 81 gm.

COLLOIDAL GOLD CHLORID REACTION.

	1	2	3	4	5	6	7	8	9	10
Cortex	4	5	5	5	5	3	3	2	1	0
Left base	4	4	5	5	5	5	3	2	1	0
Right base	1	4	5	3	3	5	3	2	1	0
Third ventricle (blood stained)	0	0	1	1	2	3	3	2	1	0
Spinal fluid (blood stained)	0	0	1	4	5	5	3	3	3	2
Pericardial fluid	0	0	0	1	2	5	5	5	5	5

*Histological Examination.—Weigert Section Left Motor Area.—*Small foci of degeneration resembling those described by Preobrajensky are noticed in the subcortical region. These, however, are not numerous. There are also some larger areas of degeneration that are in close relation to the blood vessels.

The cortical perivascular lymph spaces are distended and here and there are associated with small areas of degeneration.

Pons: Here we also see miliary foci of Preobrajensky, but these, unlike those described in Case 1, are more numerous in the peripheral portions of the medullary substance. The myelin is thinned out in many places and in many instances this has gone on to complete degeneration. Three Lichtheim plaques were counted which were in intimate contact with the blood vessels. In addition, two sharply defined areas of degeneration, involving entire tracts, are present. These are also seen in the sections of the pons stained with cresylecht-violet and are more fully described under the latter heading. The gray matter showed practically no involvement.

Medulla: The white matter showed but slight involvement. Discretely scattered between the fibers of the raphe were small foci of degeneration. In the gray matter, however, it was not uncommon to come upon distinct areas of degeneration in the neighborhood of blood vessels. This was especially true of the dorsal portion of the medulla.

Cord: In the left lateral column of the cord, in the cervical region, there are several foci of the Lichtheim type. The blood vessels which are rather numerous have greatly thickened walls. In the lumbar region, there are patchy areas where the myelin is thinned out. The gray matter appears normal.

*Cresylecht-Violet Sections—Left Motor Area.—*The pyramidal cells, especially those in the outermost layer of the cortex, are shrunken and irregular in outline, the nucleus, in many cases, being crowded to one side. In others it is entirely absent. Satellite cells are numerous. Large stellate glia cells were observed. The blood vessels are numerous and the perivascular lymph spaces are uniformly distended. The subcortical area shows no large areas of degeneration, but here and there a few small, clear areas.

Pons: Here we see many evidences of a pathologic process. In the medullary substance there are numerous sievelike areas. Here the destruction of the nerve fibers has not been accompanied by any considerable increase in the neuroglia fibers, thereby producing the cribriform appearance. One also notices large sclerotic areas which apparently are composed entirely of neuroglia. These hyaline-like areas involve entire tracts and are definitely circumscribed by fibers of other tracts which evidently have escaped being involved in the destructive process. Furthermore, these sclerotic areas are symmetrically distributed on either side of the pons. In addition to the areas just described, there are numerous perivascular areas of degeneration. These vary in size and have no definite margins, but shade off insensibly into the surrounding tissue. One of these perivascular areas of degeneration extends into a small collection
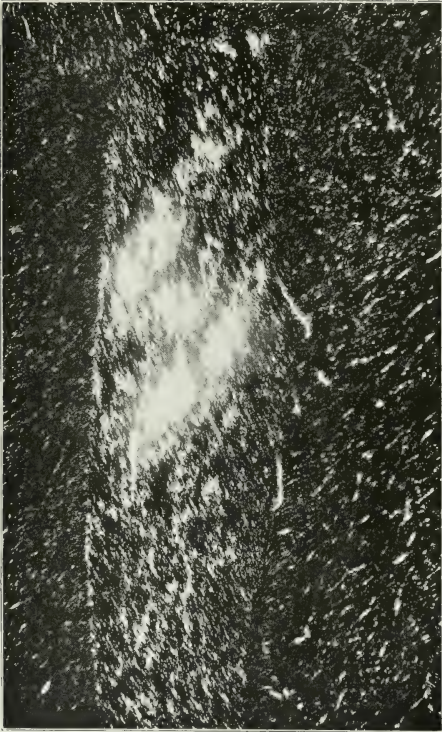
Fig. 11 (Case 2). Another section of the pons. Note the uneven demyelinization of an entire tract. The destruction has progressed very far in the center where large sclerotic areas have been formed. Compare this photograph with Figure 12, which is the same area stained with cresylecht-violet.

of nuclear cells which also show evidence of pathological involvement. They are irregular in outline. Many are shrunken and granular and some show a diffuse chromatolysis.

In the larger collections of gray matter, the perivascular spaces are distended and here and there one sees a patchy area of degeneration. These, however, are not numerous. The majority of the nerve cells show more or less changes. The axonal type of degeneration was observed.
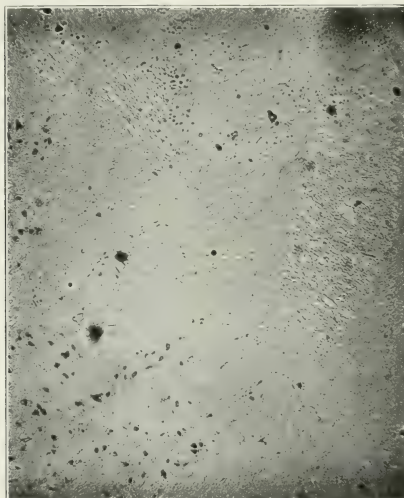
Fig. 12 (Case 2). Same area of pons as in Figure 11 stained with cresylecht-violet. This also shows the uneven degeneration of the entire tract. To its left, two other foci of degeneration are seen. (×50.)

Medulla: In the white matter, there are streaky patches of degeneration. Vacuolization is pronounced. The pyramidal tracts show no changes. Very few of the nerve cells appear normal. The majority are highly granular and show more or less displacement of the nucleus. Clear areas, that appear like rifts in a cloud, are scattered about.

Cord: Many irregular, pale areas, containing necrotic tissue and surrounded by neuroglia, can be seen in the lateral columns. In some cases, the neuroglia cells seem to be clumped together. This is also met with but to a much lesser extent in the posterior columns. The cells of the anterior horns are bizarre in shape and contain yellow pigment, similar to that described in the preceding case.

Case 3 (Necropsy 18-34). *History.*[2]—J. H., a white boy, aged 6 years and 11½ months, was admitted to the Monson State Hospital, January 15, 1917, with the diagnosis of epilepsy.

[2] This case will be reported more fully in a later paper.

Family History.—Father and mother are living and well. The father was 36 and the mother 34 years old at the time of the birth of the patient. The patient is one of seven children. One older brother, who was an epileptic, died. There is no other history of insanity or feeblemindedness in the family. An older sister of the patient died of pneumonia, aged two months. Three older brothers are living and well. The oldest, however, had convulsions when teething at one year of age and had four convulsions during the following year. He was then circumcised and he has been free from convulsions ever since. Since the patient was born, one sister has died, aged six weeks, cause unknown. One younger brother is well.

Personal History.—The patient had a normal birth and infancy up to two years, when he had his first convulsion. Teething was normal. He talked at one year and walked at eleven months. He has had no exanthemas, except chickenpox. He went to kindergarten and first grade, passed and got along as well as the other children.
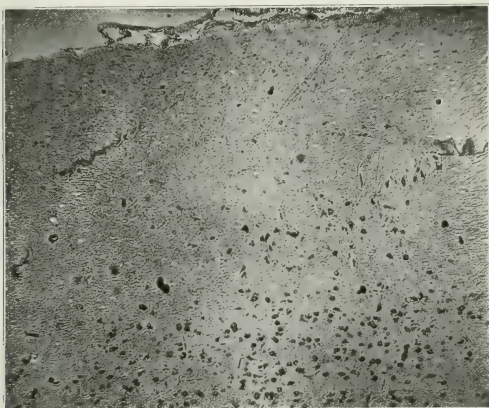
Fig 13 (Case 2). Cresylecht-violet sections of the pons. Here there are two sieve-like areas of degeneration surrounding two blood vessels. This shows beautifully the intimate relationship between the blood vessels and the "anemic foci." Evidently in a given area, some of the nerve fibers succumb to the toxic action sooner than others In this manner, no doubt, the cribriform or sievelike areas seen above are reproduced. (×50.)

Mental Condition.—Although the mother states that the patient went to kindergarten and passed the first year in graded school, he is defective in school knowledge of the first grade. He can count up to 100, but can write only the initials of his name. He can read and write no words at all. He reacts normally to the emotions and shows no other abnormal reactions except an apparent memory defect for daily occurrences. He behaves rather strangely at times, apparently not realizing just where he is going or what he is doing when out with other boys. He starts off aimlessly and apparently need supervision. Binet tests, however, show his mental age to be 6.1 years. According to the Yerkes-Bridges scale he is 7.1 years mentally. His first seizure occurred at two years of age. According to the mother's statements, the patient was in a baby carriage which was being wheeled by a young girl when the carriage suddenly tipped over. The child was apparently unhurt. Eight hours later, however, he had a convulsion which the mother attributes to the fall. There is no history of uncon-

Fig. 14 (Case 2). Another part of the same section. Here the degeneration, which surrounds the blood vessels, extends into a neighboring collection of nuclear cells. (×50.)
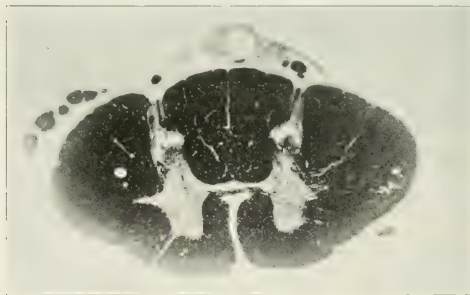
Fig. 15 (Case 2). Weigert's myelin sheath stain. Section of the cervical region of the cord showing plaques of degeneration in the lateral columns. The hole in the right lateral column has been artifically produced to indicate the right side of cord. (×10.)

sciousness or apparent injury at the time of the accident. Since that time, however, the patient has had seizures, both of grand mal and petit mal type. These, furthermore, have been increasing in frequency of late and at present occur almost daily.

Physical Examination.—The patient shows no marked asymmetry. Head measurements: circumference, 20 inches; glabella to inion, 11 inches; transverse, 10 inches. The neurological examination showed nothing abnormal. The blood Wassermann reaction was negative.

Course.—The patient remained at the hospital until June 27, 1916, and during that time had on an average ten convulsions per month. He gained in weight and height, but had made little or no progress in school. He had an attack of status epilepticus of twenty-six grand mal seizures. He was readmitted to the hospital on October 20, 1917, without any apparent change in his physical condition. He had had an attack of status epilepticus while home on a visit. A second Wassermann test was reported negative. After readmission he had less seizures, averaging only two or three each month, but he exhibited a marked change in his mentality. He attended school but without making any progress. At times he would play and associate with other children,
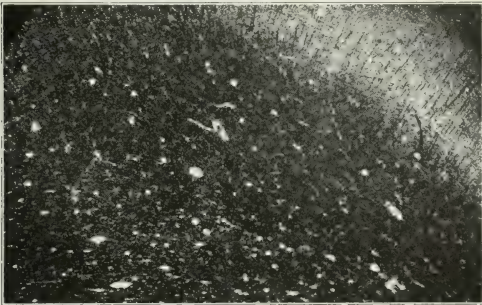
Fig. 16 (Case 3). Section of the left motor area showing numerous foci of degeneration which vary greatly in size. Weigert's myelin sheath stain.

sing songs which he had committed to memory and appear quite normal. At other times, lasting for periods which varied from a few hours to several days, he would be very seclusive; hide himself about the ward, in closets, under beds; would not associate with the other children, but would be found sitting alone quietly and if asked the reason for so doing would reply, "Other boys are rough and intend to kill me." Very often he would volunteer the information that he was going to kill himself but would not specify in what manner.

There was no marked change physically or mentally until April 16, 1918, when the patient was noticed to be suddenly acutely ill. He vomited several times, complained of headache, and there was a slight rise in temperature. By the twenty-first the condition had somewhat improved. There was no nausea or vomiting and the patient took liquid nourishment fairly well. The skin of the whole body had a marked greenish, lemon yellow tint. The mucous membranes showed marked pallor. A blood examination showed hemoglobin, 70 per cent.; 70,000 leukocytes and 2,000,000 red blood cells. The color index was high, namely, 1.75. A differential count gave polymorphonuclear leukocytes, 57 per cent.; small lymphocytes, 20 per cent.; large lymphocytes, 21 per cent.; transitionals, 1 per cent.; basophils, 1 per cent. A differential stain showed granular degeneration of the red cells, presence of nucleated reds, and also some megaloblasts.

In the night the patient was very restless and exhibited a marked psychosis. With his finger nails he tore a gash in the perineum, anterior to and extending into the rectum. He also scratched his face and hands with his finger nails.

On the twenty-fourth he was more quiet but still threatened to destroy himself and had to be restrained. The skin still retained the same peculiar hue and there were no different physical signs. Toward evening the temperature rose to 103 F., and early the next morning the patient died.

Cause of Death: Pernicious anemia.

Necropsy Protocol.—Necropsy was performed ten hours after death. External Examination: The body is that of a slenderly built, poorly nourished, white male child, nine years of age. The skin has a bluish gray appearance over the abdomen and lower chest, with yellowish cast of all muscle depressions over the chest and neck. There is a faint yellowish tinge to the sclerae. The submaxillary glands are prominent. The lymph nodes posterior to the sternocleidomastoid as well as the axillary and inguinal glands are palpable. The pupils are unequal, the right being 2 mm. and the left 4 mm. in diameter. The teeth are also unequal in size. Rigor mortis is present. The body length is 127 cm.

Fig. 17 (Case 3). Section of the dorsal region of the spinal cord. The right lateral column is principally involved. Some degeneration changes have also occurred in the anterior columns. (×10.)

Ventral Section: The fat over the abdomen is of a pale lemon color and moist. The muscles are red. The lower border of the liver is 5 cm. below the ensiform cartilage. It is brown in color. The spleen is large and free. The appendix is also free and measures 8 cm. in length. The mesenteric lymph nodes are enlarged and some are calcareous. The diaphragm arches to the third interspace on the right and to the fourth interspace on the left.

Heart: The heart muscle is firm, grayish pink in color and shows no white areas or fat.

Lungs: Both lungs showed slight congestion in the posterior portions of the lower lobes.

Organs of the Neck: The thymus is present. The tissue is stringy, but very little of the gland tissue is left.

Abdomen: The spleen shows three fetal lobulations. The pulp is firm and the malpighian bodies numerous. The kidneys show nothing abnormal. The liver weighs 1,240 gm., and a cut section looks greenish yellow. It is homogeneous, there being very scant outlining of the lobules.

Gastro-Intestinal: There were depressions in the gastric mucosae suggesting beginning ulcerations.

Head: The skull is pale in color and shows irregular thinning over the vortex and frontal region.

Brain: The dura is adherent to the calvarium. The cortex shines through a thin and delicate pia mater which is gray. The cranial nerves appear smaller than usual.

The frontal lobes appear out of proportion to the parietal. The temporal tips are unequal in pattern, the left being more complex than the right. The hemispheres of the cerebellum are also slightly unequal, the left being the larger. The brain substance is firm, especially the right frontal region. The weight of the brain is 1,280 gm., which represents a gain of 264 gm., according to Tigges' formula.

Cord: The cord shows "china white" softening in the posterior columns, especially in the lumbar region.

Histological Examination.—Weigert Sections—Left Motor Area: In the subcortical areas, the perivascular lymph spaces are distended and clear. Many small discrete foci of degeneration and four larger sclerotic plaques were noted. The cortex itself does not present anything unusual.

Pons: This section, like the two preceding sections of the pons, also contain the miliary foci of Preobrajensky. However, they are not nearly as numerous nor as universally distributed, being limited to a small portion of the medullary substance. The blood vessels in the nuclear masses are thickened and filled with red blood cells. The perivascular spaces are markedly distended, and some also contain red blood corpuscles.
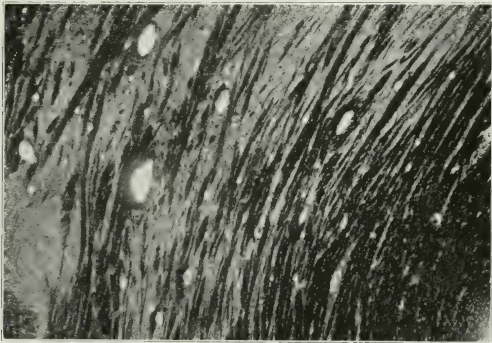
Fig 18 (Case 3). Just as in the two preceding cases, this section of the pons also shows the miliary foci of Preobrajensky. Weigert's myelin sheath stain.

Medulla: Here there is only slight evidence of pathological involvement. The lesions found are similar to those described above.

Cord: (*Cervical region.*)—In the lateral column, near the anterior horn, there is a well-defined focus of degeneration of the Lichtheim type. The lateral cerebellar tracts show patchy myelin sheath degeneration, with here and there evidence of vacuolization. (*Dorsal region.*)—Here the lesions are even more marked. The anterolateral columns show great involvement. Many foci of degeneration, including a Lichtheim focus, are seen. The blood vessels do not show any abnormalities. (*Lumbar region.*)—This section shows nothing of note.

Cresylecht-Violet Sections—Left Motor Area.—The principal abnormality noted was on the part of the pyramidal cells. A large number of these cells were shrunken and the contour of their nuclei was not clear cut. Some were highly granular and some were surrounded by satellite cells. Here and there in the subcortical area there were small vacuoles.

Pons: Here the changes in the nerve cells are similar to those just described, only much more accentuated. The axonal type of degeneration was observed. The larger pyramidal cells did not appear to be as greatly involved as the smaller.

Medulla: Here one notices large sclerotic areas which are apparently closely identified with the blood vessels. Small, clear, hyaline-like areas are fairly numerous. The nerve cells show but insignificant changes.

Cord: (*Cervical region.*)—The blood vessels are slightly thickened and the perivascular spaces are distended and filled with hyaline-like material. (*Dorsal region.*)— Here we meet with ballooning of the nerve fibers with the formation of clear sieve-like spaces. There does not appear to be an increase in the neuroglia. Many of these irregular areas are in close proximity and even surround the blood vessels. The cells in the anterior horns show a high degree of chromatolysis. Some of the cells appear to be entirely disintegrated. (*Lumbar region.*)—In this region there is very little of a pathological nature to be seen.

CASE 4.—Necropsy 16-52.—*History.*)—J. F., aged 53, was committed to the Northampton State Hospital for the Insane, May 10, 1915. The medical certificate reads as follows: "Patient is recovering from an acute exacerbation of a chronic nephritis. Patient has a cross on his arm, which he hopes will prove certain things if he can see
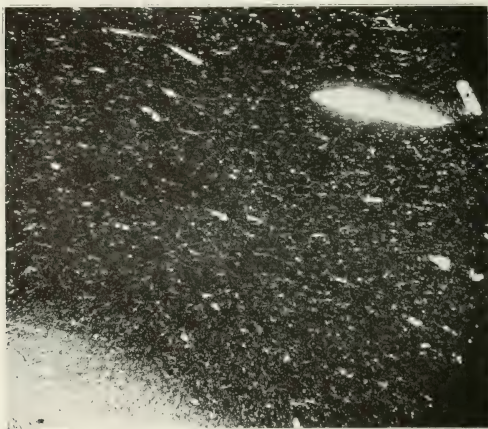
Fig. 19 (Case 4).—Numerous areas of degeneration of varying sizes are shown in this picture of the cortex. In several, the close relationship to the blood vessels is seen. Weigert's myelin sheath stain.

the priest. Wishes to see the selectmen about certain property and wishes to tell them that while there is life there is hope; that the sky is blue and other such things. Wishes to see a lawyer about disposing of his property. Is an inmate of almshouse and has none."

General Appearance.—The patient is a well-nourished, simple looking man, over 50 years of age, very anemic in appearance. During the examination he was quiet, but listless and indifferent. He did not volunteer conversation, replying correctly, however, when directly questioned. There was no stereotypy, autonomy, blocking or flight of ideas, or other abnormalities noticeable, except possibly a slight retardation. This may be his normal reaction, as he does not appear overbright.

Family History.—His father is said to have been insane. One brother is in Baldwinville (hospital for chronic infantile neurological cases), and another brother was

in the Northampton State Hospital, the diagnosis in his case being manic depressive insanity.

Personal History.—The patient was born and brought up in Ware, Mass., where he spent all of his life except for short occasional absences. He can only read and write. He was never employed except as a common laborer. He worked, however, only intermittently, and for the greater part of his life was looked after by his sister. For the past several years he has been in poor physical health. He can not state anything exact concerning this, but says that his appetite has been poor and that he believes he has kidney trouble. At one time he is said to have been very intemperate, but denies drinking to any extent for several years prior to his admission to the hospital. In 1910,
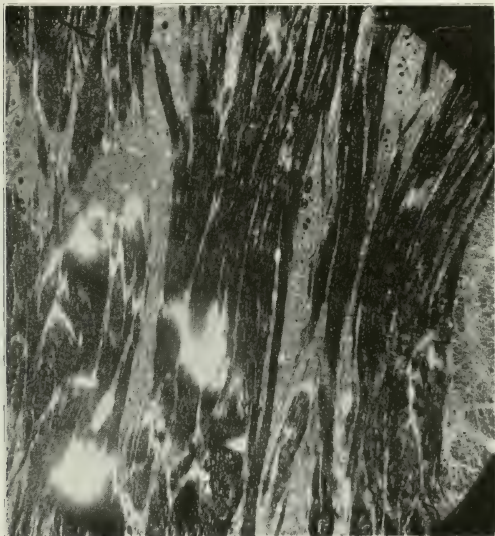
Fig. 20 (Case 4).—Weigert section of the pons. In this photograph, the Lichtheim type of focus predominates. A few of the miliary foci of Preobrajensky are also present. Note the distension of the perivascular spaces.

he was committed to the Howard (R. I.) State Hospital. The diagnosis at that time was delirium tremens. Three years later he was again admitted to the Howard State Hospital, where a provisional diagnosis of chronic alcoholism was made. The mental examination at that time showed depression and defective knowledge of current events. The patient denied hallucinations, but it was stated that a short time before coming to the hospital he heard noises on waking from sleep. He was discharged in 1914 and returned to his home from where he was sent to the Ware Almshouse. From there he was committed to the Northampton State Hospital.

Physical Examination.—A summary of the physical examination reads as follows: "Fairly well nourished male with rather poor muscular development and of decidedly

anemic appearance. The mucous membranes are very pale. There is a complaint of dyspnea on exertion and of discomfort after eating. Appears very much like pernicious anemia."

Neurological Examination.—There are no unusual phenomena observed. The patient is quiet on examination. All motions are slow and deliberate. There is no tremor or flush.

Muscle Power: This is poor.

Co-ordination: There is a slight swaying in the Romberg position, but he is able to stand without support. The gait is normal. Co-ordination tests were fairly well, although slowly performed.

Sensation: The feet and hands are slightly cooler than the other portions of the body. Stereognostic sense is normal.

Cranial Nerves: The pupils are normal in size and equal and react to light and accommodation . All the other cranial nerves are normal.

Reflexes: The superficial reflexes are entirely absent. The knee jerks are absent. The other tendon reflexes are very faint. There are no abnormal reflexes.
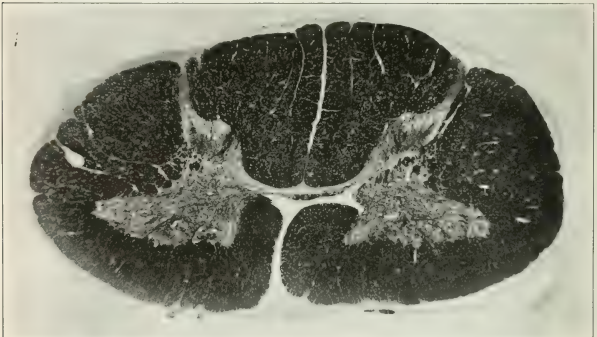
Fig. 21 (Case 4).—Section of the cervical region of the spinal cord. The posterior and postero-lateral columns are involved. A narrow strip on either side of the posterior fissure has escaped involvement in the pathologic process. Weigert's myelin sheath stain. (× 10.)

Mental Examination.—Orientation: Good in all spheres. Memory: Remote and recent memory rather poor. He remembers things in general ways but can not give details nor dates, and appears somewhat demented.

Education: He is very poorly educated. He can read and write, but has little general knowledge, and no knowledge at all of current events.

Delusions: On admission, he talked of vague unsystematized, indefinite delusions of owning considerable property which was due him from his father's estate. Mild delusions of persecution against his sister were also present, he believing that she had deprived him of his share of the estate. He made other vague statements, but his whole delusional formation was very loosely connected. He talked only when directly questioned and gave the impression of being considerably deteriorated.

Hallucinations: No definite hallucinations could be elicited. The abstract from the hospital at Howard, R. I., states that before his admission there he was hearing noises on waking from sleep. This may possibly have been a mild hallucinosis following drink.

Emotional Tone: He takes very little interest in anything about him. He shows neither exhilaration nor depression, but always appears indifferent.

Demeanor: Since his admission he has been quiet and fairly cheerful. He never volunteers conversation with anyone but answers when directly questioned.

Attention: This is fair.

Abstract of Ward Notes.—On admission, he was correctly oriented. He remembered that his brother had once been a patient at the hospital. The patient complained of not feeling well physically. He believed he had kidney trouble. He talked vaguely of his delusions and denied that he had been intemperate in recent years. He was quiet and conducted himself well. At first he helped a little in the ward when re-
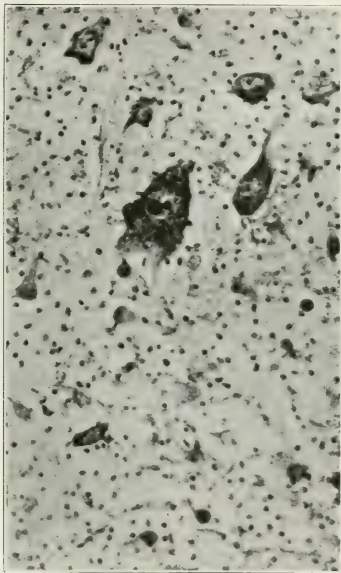
Fig. 22 (Case 4).—This is a section of the cortex stained with cresylecht-violet. A large pyramidal cell (neuronophage) can be seen which is evidently greatly swollen and undergoing degeneration. It contains two glia cells, one being within the cell body and the other within the nucleus in close contact with the nucleolus. (× 100.)

quested, but made no attempt to associate with anyone, although he could not be considered surly. When addressed, he would reply but would not continue the conversation. He took no interest in games, in reading or in the discussion of his fellow-patients. Whether this listlessness was due to deterioration or to his poor physical condition was difficult to determine.

In June, 1915, he began to complain of epigastric pain and of a feeling of heaviness following the taking of food. In September, a slight dyspnea was noticed on exertion and the epigastric distress had become so marked that he could only take

malted milk, vomiting every other food. The skin showed the peculiar brown tinge peculiar to pernicious anemia. A single blood count showed 3,260,000 red blood cells and a hemoglobin of 60 per cent. Numerous poikilocytes, microytes, and macrocytes were seen, but no nucleated reds were seen at this time. There was puffiness about the eyes. Some days he complained of weakness in the legs.

In October, physical failure became more marked. The dyspnea was so intense that care in bed became necessary. Puffiness of the eyes, hands, and feet was very noticeable. Mentally he was very dull, apparently comprehending but little. In November, 1915, a note in the history was made that he seemed slightly improved, which temporary improvement continued until April, 1916. In January, 1916, typical find-
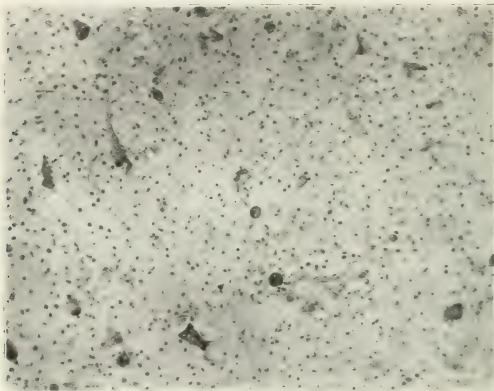
Fig. 23 (Case 4).—Another view of the cortical motor area showing disintegration of the pyramidal cells, and distention of the pericellular spaces. Some of these cells are pale, shrunken, irregular in outline, stain poorly and unevenly, and show eccentricity of the nucleus. The severe neurogliar reaction is evident. In the lower right hand corner of the field, note the large sclerotic area surrounding a blood vessel. Cresylecht-violet stain. (× 50.)

ings of pernicious anemia were present in the blood and especially the nucleated red blood cells. Early in April he failed rapidly and died on April 15, without showing any new development of his disease.

Necropsy.—Protocol (16-52).—Necropsy was performed two hours after death. The body is that of a white male, 168 cm. in length. The skin is pale lemon yellow, especially over cheeks, forehead, and arms and legs. There is considerable pigmentation over the back, chest, face and lower abdomen. Rigor mortis is present in jaws and legs. The lymph nodes are not palpable. The pupils are equal and measure 0.4 cm. in diameter. The eyeballs are slightly softened. The teeth show Riggs' disease.

Ventral Section: The fat over the abdomen is pale yellow and moist. The muscles are red and mixed with apparent fatty streaks. The lower border of the liver is 1 cm. below the ensiform cartilage. There is a slight amount of free fluid in the flanks. The appendix is 8 cm. in length. The tissue in the pelvis appears bloodless. The spleen is surrounded by adhesions. The diaphragm arches to the third rib.

Thorax: The sternal marrow is richly red and somewhat fluid. There is a free fluid in the left chest and the pericardial sac is thickened.

Heart: The epicardial fat is abundant and there are milk spots on the posterior surface. The heart muscle shows white mottling and also minute hemorrhages in the right auricle. It fragments easily.

Lungs: They show very little of note.

Abdomen: The spleen is grayish red and its capsule is slightly withered. A section shows the pulp to be red. It measures 10 by 5 by 2 cm.

Adrenals: These are small and softened.

Kidneys: There is an excessive amount of fat around the kidneys which are yellowish brown in color. The pyramids are white and poorly differentiated from the surrounding tissue. Two cysts containing fluid are seen.

Liver: There are slight irregularities over the surface of the liver which is yellowish red in color. A section shows packing together of the lobules. It measures 23 by 16 by 7 cm.

Pancreas: This organ is dotted with hemorrhages.

Gastro-Intestinal: The stomach is large and contains some fluid. The mucous membrane of the stomach is shiny.

Brain: The dura shows signs of absorption in the frontal region and of thickening along the longitudinal sinus. A slight amount of yellow fluid escapes on section of the dura. Points of hemorrhages are seen in the pia mater which shows some thickening along the vessels. It is held up from the cortex by fluid in the motor regions. The brain appears yellowish white. The right lobe sags, being apparently slightly shorter than the left. The pattern of convolutions is more nearly circular over the right lobe than over the left lobe. The brain has a resilient feeling. From the basal aspect, it is noticed that the pia is thickened over the pons, left third nerve, and optic chiasm. The left temporal tip is softer than the right. The left cerebral artery is larger than the right. The fourth ventricle is clear.

COLLOIDAL GOLD REACTION

	1	2	3	4	5	6	7	8	9	10
Right base	0	0	0	1	2	1	0	0	0	0
Left base	0	0	0	1	1	1	0	0	0	0
Third ventricle*	0	0	0	0	0	0	0	0	0	0
Spinal fluid	0	0	0	0	0	0	0	0	0	0
Pericardial fluid	0	0	0	0	0	0	0	0	0	0

* Slightly bloody.

*Histological Examination.—Weigert Section—Left Motor Area.—*The medullary substance shows little of note. Ther are a few areas where the myelin has been completely destroyed and also a few places where there is a thinning out of the myelin.

Paralleling the edge of the cortex, there is a narrow strip of tissue which stains less heavily than the surrounding tissue. Under high power, this area is shown to contain small irregular shaped spaces which for the most part are structureless. A few are crossed by undegenerated or only partially degenerated nerve fibers. In this area, furthermore, the capillaries are very numerous and the perivascular spaces are distended.

Pons: Here we see large foci of destroyed tissue in intimate relation with the blood vessels. It is almost possible to trace the entire process of their formation as they are present in all stages of development. One notices first, a slight thinning out of the myelin sheaths in the immediate neighborhood of a blood vessel. The process continues and this thinned out area becomes sievelike, due to the lack of uniformity in the destruction of the myelin sheaths. In the meshes of some of these cribriform areas, red blood cells are found. In the more advanced places, there has been an increase in the neuroglia with resultant formation of large plaques of sclerotic tissue. In one part of the field, the miliary foci described by Preobrajensky were also observed.

Medulla: Small ragged foci of destroyed tissue, irregularly distributed are seen. The perivascular spaces of the blood vessels in the olivary nuclei are markedly distended.

Cord: *(Cervical region.)*—In this region, there are numerous small foci where the myelin sheaths have been destroyed with subsequent vacuolization. This destructive process has occurred principally in the columns of Burdach. The columns of Goll are but slightly affected. The direct pyramidal tracts show more or less degenerative

changes also. (*Dorsal region.*) —This region appears practically normal. In the gray matter of the anterior horns one can see several small hemorrhagic areas. This is also present in the lumbar region which otherwise shows nothing of note.

Cresylecht-Violet Sections.—Left Motor Area.—The cortical region shows extensive pathologic involvement. There is a tremendous overgrowth of neuroglia both of the fibers and cells. The latter are encroaching on the pyramidal cells. The glia cells
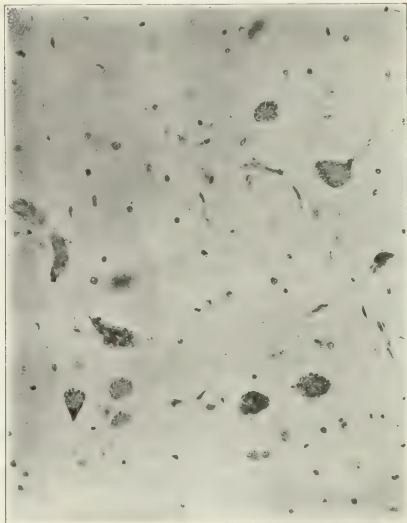
Fig. 24 (Case 1).—Section of cervical region of spinal cord stained with cresylecht-violet showing some anterior horn cells containing yellow pigment. This pigment is diffuse, slightly granular, and occupies the central portion of the cell body, the protoplasmic substance being pushed to the extreme periphery. The two cells in the lower left hand corner of the field are practically nothing but a mass of pigment. ($\times 100$.)

are of two kinds: (1) a small and apparently homogeneous cell, and (2) a large cell with a granular nucleus which in many ways resembles a small lymphocyte. In several instances these cells, both large and small, are seen to be incorporated in the body of the pyramidal cells, and in one instance one of these larger cells is seen to be incorporated within the nucleus of the nerve cell. The nerve cells, with but few exceptions, show marked degenerative changes. They are shrunken, irregular in outline, and the protoplasm is not uniform in structure. The nuclei show chromatolysis and their outline is hazy. Their position varies, being either to one side or at the end of the cell. Some of the cells instead of being shrunken are tremendously swollen. In some cases, the nerve cell seems to have disappeared entirely or fallen out, the pericellular spaces being occupied by glia cells.

The blood vessels also show a severe reaction. The perivascular spaces are distended. The capillaries show a tremendous increase. One sees them in all stages of

development, from the small, budding, rod-like projection to the thin-walled vessel with an almost imperceptible lumen.

All these pathologic changes gradually decrease in intensity as we approach the subcortical area. In the latter structure, there are many clear areas in which no nerve fibers are seen. These areas are irregular in size and shape. In the larger ones, glia fibers have replaced the nerve fibers, giving the area a hyaline-like appearance. This is brought out very distinctly with the eosinmethylene blue stain.

Right Peduncle: There is a uniform distention of the perivascular spaces, many of which are contiguous to foci of degeneration. Some of htese areas are cribriform or sievelike in appearance. The pyramidal cells show evidence of involvement. Some are completely disintegrated, some have lost their nuclei and are highly granular, and others are pigmented. Satellitosis is marked.

Pons: Small, clear, fairly regular areas corresponding, in all probability, to the miliary foci of Preobrajensky that were seen in the Weigert Section, are present in the raphe. The nerve cells do not show as great an involvement as those in the preceding sections. Only a comparative few are entirely disintegrated and none show pigmentation. The perivascular spaces are distended. There are also patches of neuroglia overgrowth.

Medulla: The nerve cells in the different collections of gray matter show uniform degeneration of varying intensity. The pericellular spaces are enlarged. Pigmentation occurs frequently. Some of the blood vessels show a thickening of the intima and a small number are surrounded by small areas of degeneration.

Cord: (*Cervical region*).—There is a sharply defined sclerotic area in the posterior column which is identical with that seen in the Weigert Section. This area is composed chiefly of massive wavy bundles of neuroglia fibers with which are intermingled an occasional undegenerated or only partially degenerated nerve fibril. The nerve cells in the posterior horn appear shrunken in size and the nuclei do not stain well. The anterior horn cells show some pigmentation. This is especially of which are contiguous to foci of degeneration. Some of these areas are cribriform true of those in the lumbar region. The character and location of this pigment are different from that of the pigment normally present in the cells of people fifty years or older. In this case, the pigment is granular, and diffusely and evenly distributed ever the central portion of the cell.

DISCUSSION

A brief résumé, contrasting the clinical with the pathologic findings reveals a fairly uniform and definite relationship. In Case 1, we can assume from the history that the condition had probably existed for about three years although a blood examination was made only five days before death. On the clinical side we find a typical blood picture of pernicious anemia; absence of all the superficial reflexes with the exception of the left inguinal reflex; absence of both patellar reflexes and sensory disturbances in the form of numbness of the feet. Mentally, the patient had visual hallucinations, paranoid ideas and mild delusions of persecution. The necropsy report showed the characteristic changes on the part of the heart and stomach. Contrasted to this clinical picture there are definite pathologic findings. In the motor area we find characteristic vascular changes, pyramidal cell changes, satellitosis, vacuolization and the presence of the Lichtheim foci of degeneration. In the pons we have in addition to the above changes the miliary foci of Preobrajensky. In the spinal cord, the posterior column is practically entirely destroyed, especially in the cervical region. Neural and vascular changes are also present. Pigmentation of the cells is pronounced and the neuroglia changes marked.

In Case 2 there is a definite blood picture of pernicious anemia. From the history we can safely infer that the condition had existed for many years.

Clinically, there are neurological disturbances in the form of hyperesthesia of the lower extremities and an unsteady gait and mental symptoms similar to Case 1, namely: visual hallucinations, delusions of persecution, and paranoid ideas. The necropsy examination revealed a pale, glassy atrophic stomach and a heart with tiger-lily striations. Histologically, the cortex showed areas of degeneration with vacuole formation, vascular changes, pyramidal cell changes, satellitosis and a marked increase in the neurogliar elements. The pathology of the pons was practically the same as that of the cortex, but again with the addition of the miliary foci of Proebrajensky. The spinal cord presented practically the same pathologic picture as the first case.

In Case 3 the clinical picture is somewhat different. In the first place the patient was very young, being about nine years old at the time of his death; in the second place he was a decided epileptic, and in the third place the onset of the pernicious anemia was acute. Hence, clinically, we have comparatively few findings. There were no neurological changes, but mentally he showed delusions of persecution and paranoid ideas. During the height of the fatal attack, he showed a marked psychosis. On necropsy, there were slight changes in the stomach, resembling beginning minute ulcerations. The heart was negative. The brain showed a gain in weight, according to Tigges' formula, of 264 gm. However, Tigges' formula is not strictly applicable to children. Pathologically, in the cortex, the changes were similar to those in the first case except that they were less marked. No neurogliar changes were seen, which was to be expected, considering the short duration of the disease. On the whole, the changes in this case were the least marked. Here again, however, the miliary foci of Preobrajensky were found in the pons.

In Case 4 the process evidently had gone on for several years. The blood picture was typical. There were marked neurological disturbances, all the superficial reflexes and both knee jerks being absent. There was also a distinct weakness of the legs. Mentally, there were paranoid ideas and delusions of persecution and other vague unsystematized delusions. No definite hallucinations were elicited. On necropsy the heart showed milk spots, white mottling, and minute hemorrhages. The mucous membrane of the stomach was shiny. The histopathologic changes were similar to those in Case 2. No Lichtheim focus was seen in the cortex. There was a marked increase in the neurogliar elements. Neuronophagic actions of the cells was marked. The pons showed the milary foci of Preobrajensky, the Lichtheim foci, vascular changes and slight nerve cell changes. In the spinal cord, the columns of Burdach showed the greatest involvement. The nerve cell changes were slight. Pigmentation was present. Also vascular changes. There was a considerable increase in the neuroglia.

The following tables show these results in tabular form:

TABLE 1.—SUMMARY OF CLINICAL FINDINGS IN THE CASES REPORTED

	Case 1	Case 2	Case 3	Case 4
1. Duration:				
(a) From symptomatic standpoint				
(b) Laboratory standpoint..	3 years	Many years	Acute	Several
2. Blood picture..............	5 days	1 year	Acute	1 year
3. Neurologic Findings:	+	+	+	+
(a) Pupils	Normal	Sluggish	Normal	Normal
(b) Superficial reflexes.....	All absent except left inguinal	Not stated	Normal	Absent
(c) Knee jerks.............				
(d) Abnormal reflexes.......	Absent	Sluggish	Normal	Absent
(e) Sensory disturbances...	None	None	None	None
	Numbness of feet	Hyperesthesia of lower extremities; unsteady gait	None	Weakness of legs
4. Mental Findings:				
(a) Hallucinations (visual).				
(b) Delusions of persecution.	+	+	None	Doubtful
(c) Paranoid ideas..........	+	+	+	+
5. Necropsy Findings:	+	+	+	+
(a) Skin				
(b) Fat	Lemon yellow	Lemon yellow	Yellowish	Lemon yellow
(c) Marrow: (a) Sternum..	Lemon yellow	Lemon yellow	Lemon color	Pale yellow
(b) Femur..	Yel. Pink	Not given	Not given	Richly red
(d) Heart	Raspberry red Enlarged white striation	Tiger lily striation; no enlargement	Normal	No enlargement, milk spots, white mottling; hemorrhages
(e) Spleen .				
(f) Liver	165 grams	185 grams	160 grams	13.5 x 10 x 1.5 cm.
(g) Stomach .	1,800 grams	1,560 grams	1,240 grams	23 x 16 x 7 cm.
	Thick walls; glossy; no rugae	Pale, glossy, atrophic	Ulcerations?	Mucous membrane shiny
(h) Brain ..	Loss 308 grams	Loss 81 grams	Gain 264 grams	Not given
(i) Cord	Minute specks of translucency in posterior columns	Not stated	China white softening in posterior columns	Not stated

TABLE 2.—SUMMARY OF HISTOLOGIC FINDINGS IN THE SERIES OF CASES REPORTED

	Case 1	Case 2	Case 3	Case 4
1. Motor Area:				
(a) Vascular changes. . . . .'		+	+	+
(b) Lichtheim foci..............		Not definite	None	None
(c) Vacuoles		+	+	
(d) Pyramidal cell changes.......	+	+	+	+
(e) Satellitosis	+	+		
(f) Neuroglia changes...........	Slight	Marked	None	Marked
2. Pons:				
(a) Miliary foci of Predohraiensky.	+	+	+	
(b) Lichtheim plaques...........	+	+	None	+
(c) Nerve cell changes...........	Not marked	+	+	Slight
(d) Vascular changes............	+	+	+	+
3. Spinal Cord:				
(a) Posterior column degeneration.		Very slight	+	
(b) Lateral column degeneration...		+	+	Slight
(c) Vascular changes............		+	+	
(d) Nerve cell changes..........		+	+	Slight
(e) Pigmentation	+	+	None	+
(f) Neuroglia changes...........	Marked	+	None	+

From the above tables, it is evident that the neuropathology of the brain in pernicious anemia is larger and more fruitful than that of the cord. It is true, of course, that all these cases showed very definite mental symptoms and hence one would naturally expect to find cortical changes. However, in the case of J. H. (Case 3), who had a definite psychosis with no neurolog-

ical disturbances, the cord changes were by far more marked and had progressed much farther than the cortical changes. From this one might argue that in pernicious anemia, the first degenerative changes occur in the cord; then the process gradually extends and involves the brain.

In the third case, there was also very little involvement of the neuroglia. This, as well as all the other points in which this case differed from the others, can be readily explained on the ground that this case had an acute onset and ran a very rapid course.

The significance of the presence of the miliary foci of Preobrajensky in every section of the pons is open to speculation. Are these lesions specific for pernicious anemia or is their uniform presence in the pons merely a coincidence? Obviously, one should not generalize from the findings of only four cases. However, to look on the regularity of their presence at merely a coincidence seems to me to be unjustifiable. At any rate, it is a point worthy of note and of further investigation.

CONCLUSIONS

1. There appears to be a fairly definite and constant relationship between the clinical symptoms and the pathologic changes.

2. The psychoses can be classified with the symptomatic psychoses of a toxic-organic nature. The whole delusional formation is vague, unsystematized and loosely connected.*

3. The brain changes are even more marked than the cord changes provided the disease has existed for a considerable length of time. This, in my opinion, is due to the fact that in addition to the toxic action of the poison on the pyramidal cells, metabolic changes also occur in the nerve cells as a direct result of the long standing anemia.

4. The blood vessels, pyramidal cells and the medullary fiber show similar degenerative changes at different levels of the central nervous system.

5. The foci of degeneration bear a definite and distinct relationship to the blood vessels.

6. In every case, the miliary foci of Preobrajensky were found in the pons.

7. Some of the nerve cells in every case with the exception of the third case, which was of very short duration, show diffuse pigmentation.

8. In speaking of the neuropathology of pernicious anemia, it is not sufficient merely to describe the lesions found in the spinal cord. The brain changes are too numerous and definite to be omitted. The neuropathology of pernicious anemia should include the entire central nervous system.

* It is quite possible that further investigation will prove that these psychoses are due to an encephalitis, and that therefore they belong in the group of encephalopsychoses rather than in the group of somatopsychoses.

BIBLIOGRAPHY

Barker, L. F.: Monographic Medicine, Vol. 3.

Barker, L. F., and Sprunt, T. P.: The Treatment of Some Cases of So-Called Pernicious Anemia, J. A. M. A. 69:1919 (Dec. 8), 1917.

Barrett, A. M.: Mental Disorders and Cerebral Lesions Associated with Pernicious Anemia, Am. J. Insan. 69:1063, 1913.

Barrett, A. M.: Mental Disorders Associated with Pernicious Anemia, Fifth Biennial Report, State Psychopathic Hosp., Univ. of Mich., biennial period ending June 30, 1916.

Berger and Tsuchiya: Arch. f. klin. Med. 94:252, 1908.

Berthelot and Bertrand: Compt. rend. Acad. d. sc. 154:1463, 1912.

Billings, F.: Progr. Med., June, 1900.

Billings, F.: The Changes in the Spinal Cord and Medulla in Pernicious Anemia, Boston M. & S. J. 147:225 and 257, 1912.

Bonhöffer, K.: Ueber psychische Störungen bei anämischen Processen, Berl. klin. Wchnschr. 48:2357, 1911.

Brown, M. A.; Langdon, F. W., and Wolfstein, D. I.: Combined Sclerosis of the Lichtheim-Putnam-Dana Type, Accompanying Pernicious Anemia, J. A. M. A. 36:552 (Mar. 2), 1901.

Camac, C. N., and Milne, L. S.: The Spinal Cord Lesions in Two Cases of Pernicious (Addisonian) Anemia, Am. J. M. Sc., 190:563, 1910.

Camp, C. D.: Pernicious Anemia Causing Spinal Cord Changes and a Mental State Resembling Paresis, Med. Rec. 81:156, 1912.

Christian, H. A.: Renal Function in Pernicious Anemia as Determined by Dietary Renal Tests, Arch. Int. Med. 18:429-444 (Oct.) 1916.

Clark, J. M.: On the Spinal Cord Degenerations in Anemia, Brain, 28:441, 1904.

Dana, C. L.: Subacute Combined Sclerosis of the Spinal Cord and Its Relation to Anemia and Toxemia, J. Nerv. & Ment. Dis., 26:1, 1899.

Goebel, M.: Rückenmarksveräuderungen bei perniciöse Anämie, Mitt. a. d. Hamb. Stattskrankenanst. 2:1, 1898.

Gordon, A.: Histological Changes of the Spinal Cord in Pernicious Anemia Apropos a Case with Diffused Degeneration, New York M. J. 90:8, 1909.

Grawitz, E.: Berl. klin. Wchnschr. pp. 704 and 730, 1898.

Hunter, W.: Pernicious Anemia, Its Pathology, Septic Origin, Symptoms, Diagnosis and Treatment, London, 1901.

Kahn, M., and Barsky, J.: Studies in the Chemistry of Pernicious Anemia, Arch. Int. Med. 23:334 (March), 1919.

Langdon, F. W.: Nervous and Mental Manifestations of Pre-Pernicious Anemia, J. A. M. A. 45:1635 (Nov. 25), 1905.

Lichtheim: Zur Kenntnis der perniciösen Anämie, Verhandl. d. Cong. f. inn. Med. 6:84, 1887.

Marcus, F. M.: Psychose bei perniciöser anämie, Neurol. Centralbl. 22:453, 1903.

McCrae, Thomas: Pernicious Anemia: The Statistics of a Series of Forty Cases, J. A. M. A. 28:148 (June 18), 1902.

Minnich, W.: Zur Kenntniss der im Verlauf der perniciösen Anamie beobachteten spinal Erkrankungen, Ztschr. f. klin. Med. 21:25 and 264, 1893; ibid, 22:60, 1893.

Moffit, H. C.: The Function of the Spleen with Particular Reference to Haemolyses and the Haemolytic Anemias, Bost. M. & S. J. 171:1639, 1914.

Moffit, H. C.: Studies in Pernicious Anemia, Am. J. M. Sc. 148:289, 1914.

Nonne, M.: Weitere Beiträge Zur Kenntniss der im Verlaufe letaler Anämien beobachteten Spinalerkrankungen, Deutsch. Ztschr. f. Nervenh. 6:313, 1894-1895.

Nothnagel's Encyclopedia of Practical Medicine, Am. Ed., 1909, Diseases of the Blood.

Osler, William and McCrae, Thomas: Modern Medicine, 1915.

Patek, A. J.: Family Pernicious Anemia, J. A. M. A. 56:1315 (May 6), 1911.

Pearce, R. M.; Krumbhaar, E. B., and Frazier, C. H.: The Spleen and Anemia, 1918, J. B. Lippincott Co., Philadelphia.

Pfeiffer, J. A.: Neuropathological Findings in Case of Pernicious Anemia with Psychic Implication, J. Nerv. & Ment. Dis. 42:75, 1915.

Preobrajensky, P. A.: Die Verändrungen im Nervensystem in einem Fälle von Anamia Perniciosa Acuta, Neurol. Centralbl., 1902, p. 727.

Putnam, J. J., and Taylor, E. W.: Diffused Degeneration of the Spinal Cord, J. Nerv. & Ment. Dis. 28:1, 1901.

Richter, E.: Ueber Spinal affektion bei letaler Anemia, Berl. klin. Wchnschr. 49:1976, 1912.

Rogers, A. W.: Disturbances of the Central Nervous System, accompanying Pernicious Anemia, J. Nerv. & Ment. Dis. 42:c93, 1915.

Schroder, P.: Herdformige Veranderungen in der Hirnrinde bei schwerer Anämie, Berl. klin. Wchnschr. 48:2357, 1911.

Shapiro: Herlung der pernicioser Anaemie durch abtreibung von Bothriocephalus latus, Ztschr. f. klin. Med. 13:1888.

Strumpell, A.: A Textbook of Medicine, Vol. 2, D. Appleton & Co., New York, 1912, p. 58.

Wiltschur: Zur Pathogenese der progressiven perniciosen Anamie, Deutsch. med. Wchnschr., 1893.

Woltman, H. W.: Brain Changes Associated with Pernicious Anemia, Arch. Int. Med. 21:791 (June), 1918.

Woltman, H. W.: The Nervous System in Pernicious Anemia: An Analysis of One Hundred and Fifty Cases, Am. J. M. Sci. 157:400, 1919.

THE TUBERCULOSIS PROBLEM IN CINCINNATI.*

B. F. LYLE, M.D.,

Cincinnati.

PART I.

While the science of eugenics is engaging popular attention and the results of the activities of the spirochetæ pallida and the corpuscles of Neisser are being disclosed to the public, the importance of the universal plague, tuberculosis, can not be obscured. The fact that the mortality from this disease in Cincinnati is large, and its relative frequency sufficiently marked to cause comment in other quarters, has been recognized by the profession and the public in general, although in no other place have there been more energetic, persevering and thorough efforts made to carry out those measures which have been regarded as efficacious in stamping out the contagion and in caring for its victims. The fact that these efforts have had little or no effect in accomplishing the desired end makes it necessary for us to ascertain the recent discoveries in the field of tuberculosis in order that we may be able to work more intelligently and hopefully. In the consideration of the subject it is important to know when and how infection occurs; if an individual once infected becomes immune to reinfection; what influence early infection has upon the subsequent course of the disease.

Fortunately the clinical manifestations of the disease do not give an adequate idea of the extent of the infection. In this paper an attempt will be made to show that tuberculosis is almost universally disseminated in civilized countries and infection occurs early in life; that the characteristics of the prevailing lesions and consequent variability and rapidity of progress depend upon heredity and the degree of communal infection; that the mortality from the disease is largely influenced by heredity, sanitation and climatic conditions; that our methods of prevention are faulty in conception and lacking in results; that while there is a possible means of prevention, it is perhaps impracticable, making it necessary for the community to wait for and depend upon inherited and acquired powers of resistance and improved sanitary conditions for general relief.

As research work in this city and country is not sufficient to enable us to interpret local conditions, I have not hesitated to appropriate any material that will assist in the presentation of the subject and have drawn largely from the papers of Prof. Roemer in the "Beitrage zur Klinik der Tuberculose."

One of the most startling discoveries of recent years is the proof that tuberculosis, like all other contagious diseases, is one of childhood and much of the exemption from its fatal consequences later in life is due to the establishment of a more or less complete immunity coupled with the pronounced natural resisting and recuperative power that is noticeable in child-

hood and continues during the period of growth. The proof that tuberculosis is almost universally disseminated and that infection occurs early in life is shown by the post-mortem findings and tuberculin tests made in many lands. As autopsy findings coupled with cultural investigations furnish incontrovertable proofs, it will be well to consider them first and also take their results as a basis to estimate the value of the less positive tuberculin tests. The most recent and authoritative are those made by Rothe, under the auspices of the Robert Koch Fund for the Conquest of Tuberculosis at the Institute for Infectious Diseases in Berlin.

Out of one hundred non-selected cases dying consecutively of various acute contagious diseases, the majority of the children being under two years of age and none over five, it was found that 21 per cent. were tuberculous; the findings were confirmed by the inoculation of guinea pigs. Gaffky, in a previous investigation in which three hundred children were examined, found tuberculosis present in fifty-seven. The work of these investigators shows that about 20 per cent. of the children under five years of age, dying from various acute diseases in Berlin, had tuberculosis of the bronchial or mesenteric glands.

As the death rate from tuberculosis in Berlin is less than that of Cincinnati (Berlin, 20.4 per 10,000; Cincinnati, 23.3), we are justified in concluding that our children are infected to an equal degree.

Hutinel, in 1895-6, in 220 autopsies of children between one and two years of age, found tuberculosis present in 33 per cent.

Kuss, in 1895-6, obtained the following results: Nothing to three months of age, 1.16 per cent. tuberculous; three to twelve months of age, 13 per cent. tuberculous; two to four years of age, 50 per cent. tuberculous.

Landouzy has found that among children dying before the second year: One in seven and one-half die of tuberculosis; one in six die of tuberculosis between birth and one year; one in four die of tuberculosis between one and two years of age; one in three die of tuberculosis between two and five years of age.

While these figures are obtained from hospital material in which tuberculosis is very prevalent, they are significant and show that the fatality from the disease increases until the third year.

Bollinger and Mueller, in 500 autopsies made in the years 1881-8, obtained the following results: Nothing to one year, 12.25 per cent. tuberculous; one to two years, 28.5 per cent. tuberculous; two to three years, 36.9 per cent. tuberculous; four to five years, 61.9 per cent. tuberculous; six to ten years, 40 to 50 per cent. tuberculous; ten to eleven years, 85 per cent. tuberculous.

Recently Benjamin and Sluka have reported the following: Nothing to three months, 6 per cent. tuberculous; three to six months, 17 per cent. tuberculous; six to twelve months, 22 per cent. tuberculous; one to two years, 42 per cent. tuberculous.

Comby, at the Congress in Washington, reported 1,447 autopsies, in 536

of which tuberculosis was found. His figures are as follows: Four tuberculous in 316 autopsies of children nothing to two months of age, 2 per cent.; 39 tuberculous in 217 autopsies of children three to six months of age, 18 per cent.; 69 tuberculous in 254 autopsies of children six to twelve months of age, 27 per cent.; 141 tuberculous in 327 autopsies of children one to two years of age, 43 per cent.

Hamberger obtained 9 per cent. of positive results in children under two years of age; Banza found 14 per cent., and Paisseau and Tixier, in the Paris clinic, obtained the following: From birth to three months, 164 cases, 12 positive, 7.7 per cent.; three months to two years, 666 cases, 141 positive, 21 per cent.

The latter have found that the results of the test in very young children are not reliable. They obtained six positive reactions from ten tuberculous children under three months of age. They find the results of their test correspond closely to the post-mortem findings of Kuss.

Cohn[11] has shown the reaction to be much more frequent in children living in a tuberculous environment. By means of the Pirquet test in 273 children of tuberculous parents he obtained the following: Two to three years old, 66 per cent. of positive reactions; four to five years old, 66 per cent. of positive reactions; six to seven years old, 77.5 per cent. of positive reactions; eight to nine years old, 77 per cent. of positive reactions; ten to eleven years old, 80.5 per cent. of positive reactions; twelve to thirteen years old, 89.9 per cent. of positive reactions; fourteen years old, 100 per cent. of positive reactions.

Pollok found 97.6 per cent. of the children in a tuberculous environment reacted, and even 96 per cent. of those two years of age were positive. These results strengthen the views of many authors that the opportunities for tuberculosis infection are as prevalent in the homes of the rich as in the rooms of the poor; when the babies live in proximity to a phthisical mother, a father with chronic bronchitis, or a grandparent with emphysematous asthma, the conditions resemble those employed for the experimental inoculation of tuberculosis.

Calmette has found that the infants thus exposed to repeated and severe infections give the following percentage of reactions: 9 per cent. between birth and the first year; 22 per cent. between one and two years; 53 per cent. between two and five years; 81 per cent. between five and fifteen years; 87 per cent. after the fifteenth year.

In Kasanlik, during the past five years, ninety-seven males have died of tuberculosis; of these, 25.7 per cent. were under fifteen years of age and 74.3 per cent. over; of the latter, 22.2 per cent. were married; 62 per cent. of these had children, and their influence upon them may be given as follows: 9.9 per cent. died before the end of the first year; 19.9 per cent. died between the first and second years; 30.7 per cent. died between the second and third years; 39.6 per cent. were living after the third year.

Children of tuberculous mothers: Of the married women, 33.2 per cent. had been pregnant. The children can be classified as follows: 16.2 per cent. died between birth and the first year; 32.4 per cent. died between the first and second year; 16.2 per cent. died between the second and third year; 34.8 per cent. lived after the third year.

When the father and mother were tuberculous, 30 per cent. of the children died of various diseases, mostly pneumonia; 60 per cent. died of tuberculosis between birth and the third year; 10 per cent. lived after the third year.

Summary.—When the father is tuberculous, 39.6 per cent. live after the third year; when the mother is tuberculous, 34.8 per cent. live after the third year; when both are tuberculosis, 10 per cent. live after the third year.

These figures are sufficient to show the prevalence of tuberculosis early in life and the reliability of the tuberculin tests.
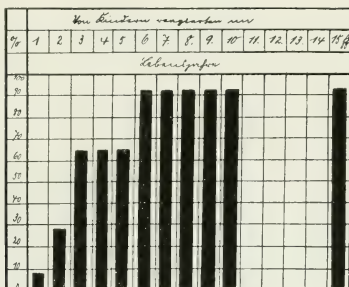
TABLE I. Results obtained by Calmette in Lille by the tuberculin test. (Beiträge Klinik der Tuberkulose.)

We are now ready to estimate the dissemination of tuberculosis in civilized countries.

Herford, from investigations made in the public schools of Altoona, Pa., has shown by the tuberculin test a minimum of 55 per cent. and a maximum of 78 per cent. of positive reactions. The children were not from the poorer classes, but from families in moderate circumstances. The higher figures were naturally obtained in those children who were in contact with tuberculous relatives. He arrives at the conclusion that the majority of children are infected before they enter school; 2,598 children were tested with 20 per cent. tuberculin.

In Bucharest, Nicolaesco and Nestor tested 2,000 children by the conjunctival method; between 65 and 66 per cent. were positive.

Calmette got like results from the Pirquet test in Lille in children of the working classes. They show from birth to one year, 8 per cent. positive; one to two years, 28 per cent.; two to five years, 65 per cent.; after the sixth year, 92 per cent.

These figures, from Altoona, Bucharest and Lille, are like those obtained from Vienna, Prague, Danzig, Paris, Dusseldorf, Berlin and Muenchen, and indicate how universal is the saturation of children with tuberculosis in cities.

Scheltema found a somewhat lower proportion in the tuberculin tests of 520 children in the Groninger policlinic. He thinks this is due to the better character of the dwellings.

In this work there has been a noticeable void because of a lack of investigations made in the country. Formerly we had only the careful investigations of Hillenberg, who, apparently, did not adopt the best method.
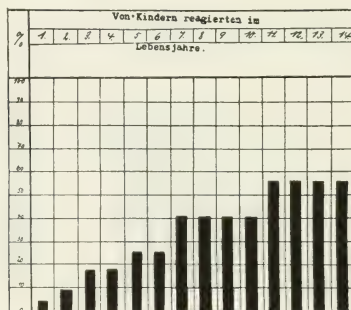
Table II.—Results obtained by Scheltema from the tuberculin test in Groningen.
(Beiträge Klinik der Tuberculose.)

Jakop recently attempted to determine the extent of tuberculosis in the country surrounding Hanover. He gave the Pirquet test to 2,744 children; 1,927 were between six and fourteen years of age and 817 between six months and six years. The responses from those attending school was 45.9 per cent. In the first year of school it was 35.6 per cent.; in the last, 64.4 per cent. Jakop gives no reason for inferring that the infection occurred in school and has concluded it was contracted at home before attendance at school. These figures also prove that tuberculosis is but little less prevalent among the country folk than among the children in large cities.

The observations of Jakop are conspicuous in showing that when tuberculosis was present in a house the children nearly always reacted; again,

there were children who reacted for whom he could find no source of infection. In cottages where there had been no one sick with tuberculosis for years 30 to 40 per cent. of the children recated. This is a proof of the remarkable diffusion of the yet unrecognized occasion for infection. Hillenberg, in more recent investigations, obtained like results. He worked in a region where tuberculosis was not very prevalent; the mortality from tuberculosis being but 9 per 10,000. According to the statement of Koch this is the lowest in Germany. Hillenberg, in six country areas with an almost exclusive farming population and satisfactory dwellings, prosperous inmates and good sanitary arrangements; for cleanliness being also fairly good; a region where for ten years there had not been a death from tuberculosis discovered; yet found 25 per cent. of the school children reacted to tuberculin. A source of infection from coughing consumptives was excluded and likewise infection from cattle. As a result Hillenberg came to the conclu-
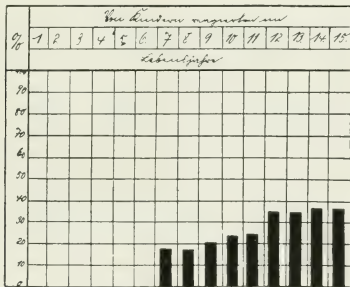
TABLE III.—Results obtained by Hillenberg in rural districts in Germany. (Beiträge Klinik der Tuberkulose.)

sion that here, as in similar instances, the tubercle bacilli in nature must have a wider scope than is usually recognized.

"From a practical epidemiological standpoint one can hardly speak of anything more than an ubiquitous extension."

Roemer believes it possible that those infected with latent tuberculosis may be able to spread the disease in a manner that is incomprehensible to us at the present time. This, of course, is a pure hypothesis based upon the results of veterinary practice and his own observations. It can at times be shown that the introduction of a tuberculous cow into a previously tuberculosis-free stable leads to a gradual involvement of the entire herd to the extent that suddenly nearly all react; although this need not indicate that

the imported beast is tuberculous in a clinical sense if the employment of other means of proving the presence of tubercle bacilli are negative.

Hillenberg further investigated by examining the remainder of the people in these communities and occasionally, though rarely, found a case of tuberculosis by means of the pirquet test. He found conditions to be as seen in the following diagram. At the conclusion of childhood he shows that 36.4 per cent. of the children were infected. The results in the several regions varied from 10 to 61.7 per cent. These figures are lower than those obtained in the large cities. It may be observed that Hillenberg carried on his investigations by the cutaneous method. Roemer believes that a more sensitive method would have shown a larger number of positive findings. Hamberger and Monti, when examining children between the ages of eleven to fourteen, with the cutaneous method, got 52 per cent. of positive reactions, but by the united cutaneous and puncture method 95 per cent.

AGE	TOTAL DEATHS	TUBER-CULOSIS	RATIO	
Under 16 years	18545	767	4.2%	
15 to 19 years (inclusive)	1603	490	30.6%	
20 to 29 years	5658	2331	41.2%	
30 to 39 years	6254	2073	33.1%	
40 to 49 years	5827	1257	21.6%	
50 to 59 years	5728	648	11.3%	
60 to 69 years	6423	352	5.5%	
70 and over	8294	140	1.7%	
White	94609	7067	13.0%	
Colored	4620	901	19.5%	
Males	31497	4716	18.0%	
Females	37137	3341	12.3%	
Total	68634	8058	13.74%	

TABLE SHOWING THE NUMBER OF DEATHS DURING EACH
A 5 PERIOD FROM ALL CAUSES AND TUBERCULOSIS
AND THE RATIO OF THE LATTER TO THE TOTAL MORTALITY.

Tuberculosis ☐ Other causes
Table based on death returns of Cincinnati from 1894 to 1903.

TABLE IV.—Showing comparative mortality from tuberculosis in Cincinnati at various periods.

In Nothmann's investigations positive results were increased in 263 cases from 47.1 per cent. by the cutaneous method to 77 per cent. by the stick method. Even if the experiments of Hillenberg in the sparsely tuberculous areas indicate that the degree of involvement is not so great as in the large cities, we learn, on the other hand, the surprising fact that even in those places where tuberculosis is so rare opportunities for infection must be at the same time considerable.

The enormous percentage of reactions that may be obtained in the children in a tuberculous environment is shown by the comparative tables of Cohn.

All these results strengthen the view that the opportunities for infection are so widespread that, at least in neighborhoods with a high morbidity from

tuberculosis, all children at the termination of childhood will be infected with tuberculosis.

If it is a fact that this tuberculosis saturation is almost universal so early in life, it will be interesting to know why the period of greatest mortality is so far removed; at least a score of years.

That this is true is seen by our own records and those of other countries. Infection that is severe enough to be manifest almost invariably leads to a fatal ending if it occurs before the first year; after this there is a period of fifteen years when the mortality from the disease is comparatively slight, although tuberculin tests prove the presence of tuberculosis in a latent state.

This condition is not without advantage to the individuals infected, for we learn from animal experimentation, clinical, epidemiological and statistical findings that protection is thus afforded against a further tuberculous infection and an immunity is established of a greater or less degree, which, in the majority of cases, confers exemption for life from the serious consequences of the disease; and, in the majority of the others, the clinical course and pathologic lesions are so changed that we find the duration of the disease much longer and the anatomical appearances entirely different from those characteristic of acute tuberculosis.

It may be of value for us to here consider more fully the advantages we thus enjoy from a danger from reinfection and the effects of more acute and fatal forms of the disease.

A number of experiments have been made on animals, ranging from guinea pigs to monkeys, to learn the degree of resistance of the tuberculous to a further implantation of germs.

The experiments made upon cattle some time ago by Marburger prove that an artificial infection with virulent tubercle bacilli confers immunity against a new infection. These facts have been recently confirmed and strengthened by Finzi in experiments upon eight calves suffering from spontaneous tuberculosis. These experiments are important as they confirm the findings made upon artificially infected animals.

The same results were obtained previously by Vallee and Calmette and finally Roemer has shown there can be no doubt as far as animal experimentation can show that an existing infection, either natural or artificial, is a protection against further infection. He first inoculated guinea pigs, but, because of their great susceptibility, concluded his experiments with sheep. He finds, however, the immunity is only relative and a very heavy assault can cause the immune body to succumb, even if at a much slower rate than occurs in the non-immune animal.

It is now proven by animal experimentation, and confirmed by a large series of statistics, that a strong infection in a partially immune organism leads to forms of tuberculosis that are entirely different from the results of a primary infection, and it is because of this that human tuberculosis can clinically and anatomically exhibit very dissimilar disease aspects; the view is also permissible that through this strong immunity the organism can over-

come a severe infection. Roemer believes it must be accepted that the effectual reinfection leading to phthisis does not originate outside, but must be already present in tuberulous foci; in other words, it is a metastatic auto-inoculation. There are difficulties in explaining these conditions.

A reinfection that may be interrupted in adults results in a child in a marked degree of involvement. Roemer, in co-operation with Joseph, has established that the immunity of tuberculous individuals against a new infection in many cases does not depend upon a destruction of the newly introduced bacilli; at least, in animals proven to be immune by reinfection, living bacilli could be shown at the place of inoculation. Again, the serum of highly immunized sheep was not able to destroy the tubercle bacilli in a single instance under favorable conditions.

Roemer believes the immunity to be a labile one and resembles the form of immunity we see, for example, in the perophasmodium of cattle (Texas fever). Animals that have overcome the acute infection remain infected with the living virus but are immune to a new infection and can remain without danger in infected meadows.

We must presume that tuberculosis immunity is specific in nature, although not marked as in the cases of more acute diseases; the intensity of immunity usually being in proportion to the sensibility of the individual to the contagion.

The fact that tuberculosis is a disease usually contracted early in life makes the environment the chief predisposing factor. Investigations have shown that in 50 per cent. of the active cases of tuberculosis in children a parent had open tuberculosis.

What had been regarded as predisposing factors in the causation of the disease we may now consider agencies, which, by reducing the inherent or acquired immunity, permit what would be a latent process to become active. If we were to attempt to individualize these pernicious agencies, although they are characterized by team work, half a dozen or more could be selected, any one of which is sufficiently important to be considered the principal and all must receive practical attention before the dawn of the non-tuberculosis era. Without attempting to cover the field we may mention poverty, alcoholism, the location and character of dwellings and shops, unsanitary occupations, particularly those of the "blind-alley" kind; child labor and long hours of labor.

These are factors because of the chronic nature of tuberculosis. They are not predisposing causes, except in so far as they may be instrumental in increasing the sources of contagion. Ignorance and overcrowding are important but not essential factors in all contagious diseases. It is interesting to notice the influences attributed to heredity at different times. At first it was regarded as the most important element in the origin of the disease; then it was maintained that a peculiar vulnerability of a specific character was transmitted from parent to child; today it is regarded of importance because of the immunizing capabilites that are transmitted. The individual

is not supposed to be protected from the infection, but is shielded by a partial immunity manifested by a difference in the nature of the lesions induced; they being of a much more chronic type; the life of the victim is thus frequently spared at a cost of physical vigor and frequently he is held as a hostage for the dissemination of the germs. That the influence of heredity is potent is attested by many recent investigations.[12]

We are therefore forced to the conclusion from a study of the relative mortality from the disease and the variety of its manifestations in various peoples and races that heredity must play an important part in determining the character of the lesions and the percentage of mortality. We find this is also true of the contagious exanthemata; the Chinese and Japanese being exempt from scarlet fever, while the natives of newly discovered islands die in great numbers when they are first infected with hitherto unknown contagious diseases. The Jewish people from a long familiarity with tuberculosis enjoy a comparative immunity from its fatal consequences, although they evidently possess no exemption from manifest infection.
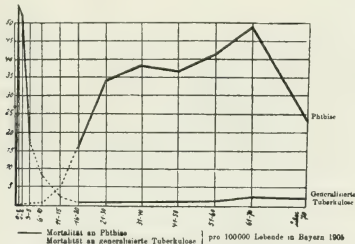
TABLE V.—Showing the relative proportion of the acute and chronic forms of tuberculosis at various ages in civilized countries. (Beiträge Klinik der Tuberkulose.)

Rothe is of the opinion that the early infection results in the establishment of an immunity that protects the majority of persons from any further manifestations of the disease and in others leads to a marked prolongation of the evolution of the pathologic process. He believes that as in syphilis we find various phenomena making their appearance in a fairly orderly succession, due to the gradual involvement of tissues that at first were invulnerable, so in tuberculosis do we find a like condition.

Thus, we can differentiate: First, a stage of generalization (glandular tuberculosis) having an origin directly from the infection; second, a stage of hematogenous dissemination, characterized by scrofula and bone and joint involvement; later, we have phthisis with its sequelæ, involvement of the larynx and intestines and other organs.

That exemption from the more acute extensive tuberculous processes characteristic of the disease in the non-immune individual is due to the protection secured early in life is shown by the clinical aspects of the disease in sparsely settled countries and among those races which have but recently been brought into contact with the disease.

If the tuberculosis does not cause a rapid death it leads to increased resistance against tuberculous infection, thus preventing contagion from the outside later in life. The degree of immunity is not sufficient to destroy the bacilli present and the involvement of organs later must be the result of auto-infection. We have an analogy of this in malaria.

Roemer approves of the conclusions of Hamberger, whose observations showed that after a reinfection of guinea pigs the place of inoculation remains for a long period reactionless; but, however, when for any reason the immunity is lost, even after a series of months, the hitherto weakened tubercle bacilli gain the upper hand and cause an exacerbation of the tuberculous processes.

Numerous individuals, in spite of such reinfection, do not become phthisical. There is also reason for maintaining that certain groups of individuals are also immune to tuberculosis. It is no doubt true that children who suffered from a relatively severe infection in childhood are more prone to positive results later in life, due to metastatic auto-inoculation.

In 1908-10, Freymuth examined the histories of 1,400 adults and 328 children; as a result, he came to the important practical conclusion that it can not be acknowledged that there is any necessity for the separation of open and closed cases in a sanatorium.

The most startling investigation in this line is the work of the Japanese, Kurashige, who, by means of a modified anti-formin process, found bacilli in the blood of 155 tuberculous patients in various stages; not only this, but in twenty of thirty-four investigations of clinically healthy adults (59 per cent.) he found tubercle bacilli in the blood. In four the findings were confirmed by inoculations in guinea pigs. These results were confirmed by Luzuki and Takaki, who found tubercle bacilli in the blood of 509 out of 517 tuberculous patients and in twenty-eight out of fifty-four clinically healthy men. These twenty-eight gave a positive Pirquet and in none of those who did not react were the bacilli found in the blood.

This shows the fallacy of the old belief that bacilli in the blood leads to miliary tuberculosis. It shows there is no correspondence in the results of the inoculation of normal animals and those who are already infected. Acs-Nagy, months before the demise of patients, found tubercle bacilli in the blood without miliary tuberculosis resulting. It has been maintained that the progression of the bacilli in the various organs varies greatly, according as the implantation is introduced into a normal individual or into one with tuberculosis. This is shown by epidemiologic examinations.

PART II.

In countries in which there is a comparatively slight amount of tuberculosis in adults we more frequently see the more acute forms of tuberculosis characteristic of childhood. In this connection the observations of Deyckes in Turkey, of Romer and Nine in Argentina, and of Westenhoeffer in Chili, are confirmatory. In autopsies made by the latter, in Santiago in 1908-9, he found the dissemination of tuberculosis to be much less than is seen in the post-mortems of European pathological institutions. Not more than half the amount was found and there was a remarkable difference seen in the forms of the disease. In forty-five who had died of pulmonary tuberculosis only twenty-eight had the chronic form and even in these there was a failure of connective tissue formation and large cavities. The majority of the cases were of confluent caseous pneumonia, a form of tuberculosis we are accustomed to see in the children of Europe. Westerhoeffer says that at least one-third of the cases are of very acute forms. He ascribes this difference to the fact they have not had the early protection of a latent form acquired in childhood.
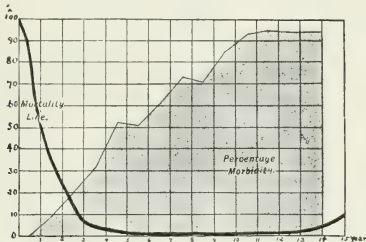
TABLE VI.—After Escherich. Showing the relative mortality and morbidity in children in Vienna in 1909. (Wien. med. Woch.)

In support of this the observations of Metschnikoff, Burnet and Tarassevitch, made in Russia, are important. They found that the sons of Calmuck families, when sent to the more advanced schools of Astrakan, died at an astonishing rate from acute tuberculosis. Phthisis was relatively rare. Like observations were made by Metschnikoff and others in Austria which show that in the regiments sent from Bosnia and Herzegovina the soldiers died with greater relative frequency from tuberculosis, notwithstanding the fact that the disease is not very prevalent in their own provinces.

These observations help us to solve a problem with which Koch was busy in his last years. It is known that in Germany and in other civilized countries the death rate from tuberculosis has decreased since 1880, while in Norway, Ireland and Japan it has increased. The above epidemiological

experiments, taken with the tuberculosis immunity observations, offer the key to the still unsolved problem.

"The less prevalent tuberculosis is among a people the greater is the toxicity of the disease." That is, increased mortality to morbidity. This indicates the presence of the more severe acute forms of the disease in a slightly contaminated population, either from rarity or failure of the milder chronic phthisi.

As a result we may express the formula, "The more widely spread the tuberculous infection the less the relative mortality." The meaning of these two precepts is appreciable when we remember the facts tuberculosis immunity represent; that is, keep in mind that the tuberculous individual is apparently protected from outside new infections. The auto-infection from within, even if severe, shows there is a relative immunity in that not a galloping consumption but a chronic phthisis ensues.

By means of this resistance in those countries in which tuberculosis is the most extensive; in which tuberculous saturation has reached its highest tide, the mortality rate from tuberculosis had materially declined.

The accompanying charts, showing the tuberculosis record of Hamburg for the last ninety years, proves this conclusively.

Of course, we are apt to consider that the significant and remarkable changes in the mortality rates of an epidemic scourge depend upon artificial influences and it is humanly comprehensible that even medicine is willing to claim that the credit for these improvements is due to her own scientific acquisitions.

No doubt, however, were the history of plagues better known and the variations in the intensity of infectious diseases better comprehended we would not agree too lightly to such claims.

We are reminded here of the disappearance of the plague from Europe at the beginning of the eighteenth century, the reason for which is not clearly understood, and remember how often, still earlier, when the epidemic was absent for one to ten years, in every instance the methods employed were promptly credited as the cause. We are cognizant of the remarkable changes in the mortality rate of smallpox in very recent years. Finally, we may refer to the experiences of life insurance companies obtained in an experimental way. They do not reject individuals who are free from a history of hereditary tuberculosis and whose personal record is clear when they are living or have lived with a tuberculous partner. Little regard is paid, at least in Germany, to the danger of an adult living with a tuberculous mate, and one can not accuse the insurance companies of being careless.

In conformity with this is the record of so experienced a physician in tuberculosis as Petruschky. When mentioning the dangers that marriage brings to the tuberculous he touches upon the danger of infection through the tuberculous partner and states as laconically as impressively: "From reports not yet observed." In this connection we can state that before the discovery of the tuberculous germ many physicians did not believe in the con-
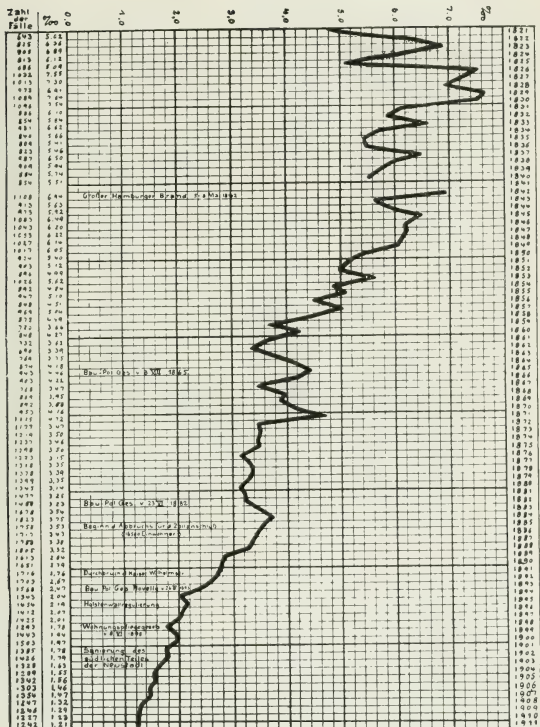
TABLE VII.—Showing progressive decrease in mortality from tuberculosis in Hamburg during the past ninety years. (Beiträge Klinik der Tuberkulose.)

tagiousness of tuberculosis because they saw many persons remain in close contact with consumptives without apparent injury.

In striking contrast to this are the recently reported investigations of Jakob, made in a badly infected region in the neighborhood of Osnabruck. He mentions the danger that might arise through dwellings and makes the following observations: The wife of a healthy man died of consumption. Some time after he married again and this wife died from the same disease. The same occurred with the third and fourth wives. Jakob thinks this resulted from a house infected with tuberculosis. It is remarkable that the husband remained well in the house and Jakob states he has never seen the second husband of a healthy wife die of consumption whose first husband had died from the disease.

Metschnikoff, Burnet and Tarassevitch, in the report of their work, mention a similar observation.

One of the authors of the book lived for a year with his wife, who had a fatal form of consumption, without contracting the disease.

Why is it that a house that is infected sufficiently to be fatal to the incoming wives was not fatal to the husband?

It may be remarked that Jakob indicates the marked prevalence of tuber-culosis in the people of this region, so that it is plausible that the man in every instance had married an infected woman in whom pregnacy, childbirth and the puerperal state had favored the progress of the disease. The objection that it was a peculiar coincidence that a man should marry a tuberculous woman in every instance appears out of place. The consumptive Venus of Botticelli was regarded for years as the ideal of a perfect female form; therefore, why should there not today be an individual who ignorantly and fatefully turns only to a consumptive type? Finally it must be mentioned that Jakob, as a result of his careful research, is of the opinion that the infection during childhood, as a rule, potently influences the after-life of some persons.

The fact thus proven by clinical, epidemiological and statistical investigations that adults enjoy an appreciable or even absolute protection against a new infection from without emphasizes the fact that when children they had a mild infection.

What shall we say about the tuberculosis situation in Cincinnati? What are the results of the measures that have been employed? What course shall be pursued in the future?

In the decade, 1901 to 1910, the death rate in the United States from tuberculosis declined from 196.9 for each 100,000 to 160.3, a decrease of over 18 per cent.; while the general death rate from all causes declined only half as much, at the rate of 9.7 per cent., or from 1655.0 to 1495.0 per 100,000.

We are informed by Dr. Maurice Fisher that in Germany within the last five years the mortality from tuberculosis has ceased to fall.

Prof. Walter F. Wilcox, of Cornell, consulting statistician of New York State, in his reports for the years 1909 and 1910, states that the campaign against tuberculosis has as yet made no change in the tuberculosis mortality of New York State.

A glance at the death statistics of our city shows that the mortality from tuberculosis bears a certain relation to the general death rate. In other words, any measure or condition that influences the death rate in the city has a proportionate effect upon that from tuberculosis. The rate among children seems to be greatly reduced. This seems somewhat remarkable when we bear in mind the results of the observations of Landouzy and other Continental writers, although they correspond to the observations noted recently in Switzerland.

It is very difficult for us to determine the mortality from tuberculosis among children previous to the beginning of this century, owing to the fact

Tuberkulosesterblichkeit in der Stadt Hamburg.
Auf je 1000 Lebende derselben Altersklasse
starben im Alter von ·

0-1-8 J. — 18-20-25-30 J. 30 — 50 J. 50 — 70 J. über 70 Jahre

w. ----- 1872–1898.   w. ••••• 1899–1910.
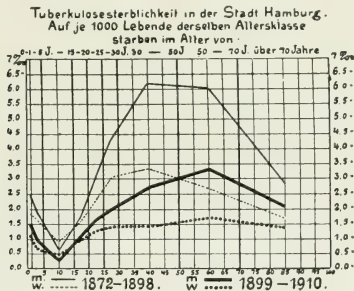
TABLE VIII.—Showing the influence on adult mortality of tuberculosis at various periods. (Beiträge Klinik der Tuberkulose.)

that our health office reports show that about the year 1880 hydrocephalus prevailed to a great extent and was classified as tuberculosis. Ten years later this uncertain term had given place to marasmus.

Prof. P. G. Woolley, who kindly glanced over the statistics, advised the exclusion from the list of deaths from tuberculosis those which were attributed to these causes in children under one year of age.

In the first period shown no records can be found of extra-pulmonary forms of tuberculosis. The same proportion as given in the following decade was used in order to obtain an approximate estimate of the total deaths from tuberculosis.

In order to make the estimate as reliable as possible the records of the census years and the two years preceding and following were taken and

the average employed. The great mutations seen make this necessary if we aim to secure reliable data.

These statistics show that the general death rate in our city has been progressively reduced, no doubt due largely to the diminution of the mortality among children.

The present tuberculosis death rate is higher than that of the previous

Table Showing Death Rates for Census Years and the Two Years Preceding and Following, with Averages.

Year	Total deaths	Total number of deaths from			Ages of children dying from tuberculosis			
		Tuberculosis	Pulmonary	Extra-pulmonary	1-5 years	5 years	10 years	15 years
1868	4424		443					
1869	3740		447					
1870	3978		582					
1871	5291		580					
1872	5116		616					
Av.	4510	*576	534	*42				
1878	4823	705	659	46	52	22	10	17
1879	5290	740	698	42	55	22	9	5
1880	5177	771	720	51	53	17	17	8
1881	6110	997	904	93	81	38	14	14
1882	6873	846	783	63	59	26	17	17
Av.	5653	812	753	59	60	25	13	12
1888	5994	903	746	157	75	20	21	18
1889	5922	878	731	147	60	28	12	16
1890	6441	913	756	157	58	22	15	19
1891	6635	700	643	57	46	26	18	12
1892	6015	817	647	100	61	31	13	14
Av.	6201	842	704	138	60	25	16	16
1898	5885	729	642	87	22	16	16	14
1899	6000	804	692	112	39	21	7	14
1900	5412	714	635	79	24	16	9	9
1901	6155	822	742	80	14	19	14	9
1902	5744	736	647	89	22	14	3	11
Av.	5839	761	672	89	24	17	10	11
1908	6449	952	860	92	21	13	10	13
1909	5921	947	850	97	39	20	9	12
1910	6330	1025	912	113	35	19	12	12
1911	6225	986	876	110	21	13	10	13
1912	6453	968	856	112	33	18	10	12
Av.	6278	976	871	105	30	17	10	12

* Extra-pulmonary forms not recorded and same proportion given as in following decade

decade and the same that prevailed forty years ago, before Koch discovered the specific germ and fifteen years after Villemin had established the contagious character of the disease. The diminution in the deaths from tuberculosis has not kept pace with that of the general death rate.

Dr. Schmid, director of the Swiss Health Office at Berne, states that tuberculosis has decreased in Switzerland since the middle of the eighties. This decrease is especially noticeable in the younger element of the popula-

Table Showing Average Death Rates of Various Periods and Giving the Ratio of Deaths from Tuberculosis to the General Death Rate and to Population

Census	Population	Average death rate of each period from				Ratio of mortality from the to total death rate	Ratio of mortality in every 10,000 of population from	
		From all causes	Tuberculosis	Pulmonary	Extra-pulmonary		All causes	Tuberculosis
1870	216,239	4510	*576	534	*42	.127	208.6	26.6
1880	255,139	5653	812	753	59	.144	221.9	31.8
1890	296,908	6201	842	704	138	.136	208.8	28.3
1900	325,902	5839	761	672	89	.13	179.1	23.3
1910	364,463	6278	976	871	105	.155	172.0	26.8

* Extra-pulmonary forms not recorded and same proportion given as in following decade

tion, while it has increased in those above sixty. The most remarkable decrease has been in children in the first five years of life. Out of 10,000 there were 29.0 deaths in 1901; this fell to 18.4 in 1908.

While our records in Cincinnati are confusing on account of the peculiarities in nomenclature or divergent views as to the significance of clinical conditions, an examination will show an apparent diminution of the number of deaths among children. They prove this not only to be true of tuberculosis, but of other diseases. In 1886 the deaths among children under five years of age constituted 42.86 per cent. of the entire mortality rate; the ratio for the city being 18.98 per 10,000. In 1911 the deaths in the early years of life had been reduced to 17.26 per cent. of the whole, the general mortality rate being 17.23 per 10,000. This makes very pertinent the inquiry: Does not the favorable showing depend upon this enormous saving in the lives of children?

A close study of these statistics will indicate that they are more significant than surface indications show. An investigation which I made in order to estimate the comparative death losses of various parts of the city showed the average loss per 10,000 to be 22.5; in the oldest portion of the city near the river it was 38.0; the average of the rest of the basin and the hillsides was 22.2; while on the hilltops the rate was only 12.5.

We must now recall the fact that in 1870 Walnut Hills was the only large suburb. It had a comparatively small population which depended upon omnibuses for transportation. Ten years later the same conditions prevailed. Horse cars began to go to Walnut Hills about 1880. Before 1890 the boundaries of the city were extended and suburban areas with small death losses from tuberculosis were absorbed. The advent of the electric cars before the next decennial and the inclusion within the city limits of large suburban areas still further enlarged the areas of the city favorable for residence purposes.

During the past ten years conditions favoring a choice of suburban homes have improved; notwithstanding the death rate from tuberculosis has increased.

This is possible because sanitary measures, though indispensable and invaluable, do not prevent infection. It will be well to consider this aspect of the subject in order that our views on the prevention may be made more definite.

It seems somewhat incomprehensible that at an almost legally established time at the conclusion of the body maturity a large reinfection or rather recrudescence of the disease should occur.

It is not possible to give a complete satisfactory explanation of this, although it may not be particularly remarkable that at such a period of life with such pronounced evolutionary changes in the organism that many slumbering germs in the body find conditions favorable for development.

Hart believes that he has found the lacking scientific explanation, and suggests that important mechanical incongruities in the region of the upper thorax lead to the causation of pulmonary tuberculosis.

That this view is not generally accepted is shown by the position of Reiche on the heredity of chest conditions predisposing to lung phthisis, and further on the importance of the habitus paralyticus and its extent in phthisical families. He thinks it will be necessary to know whether it is a cause or an effect before we can decide.

Pottengers' observations are in striking contrast with the views of Hart and Freund as to the cause of changes in the upper thorax cavity so frequently found in consumptives. He believes them to be due to the tuberculosis. Williams years ago established the fact that even in early tuberculosis a hypertonicity of the muscles of the diaphragm caused a diminished movement upon the diseased side and was an early diagnostic sign. Pottenger holds that this hypertonicity involves all the muscles of respiration on the involved side, particularly those of the neck. This muscle spasm disturbs the movements of the upper part of the thorax causing a narrowing of the intercostal spaces and anchylosis of the costo-sternal and manubrio-sternal articulations. He also believes a careful observation of the appearances of the upper portions of the chest will convince one that the relations between the tuberculous lung involvement and these abnormalities is one of cause and effect.

The doctrine of the importance of the paralytic thorax for the development of phthisis, on the one side, and the theory of the influence of early infection as a factor for the development of consumption in adults, on the other, are somewhat bridged over by these new views.

Pollak, a pupil of Hamberger, brings proof that it is not always true, as has been maintained, that infection in the first year always causes death. He shows that a third of those infected go over into the second year without offering any prognostically bad symptoms. He believes that infected infants that do not die of the disease gradually acquire a typical tuberculous habitus.
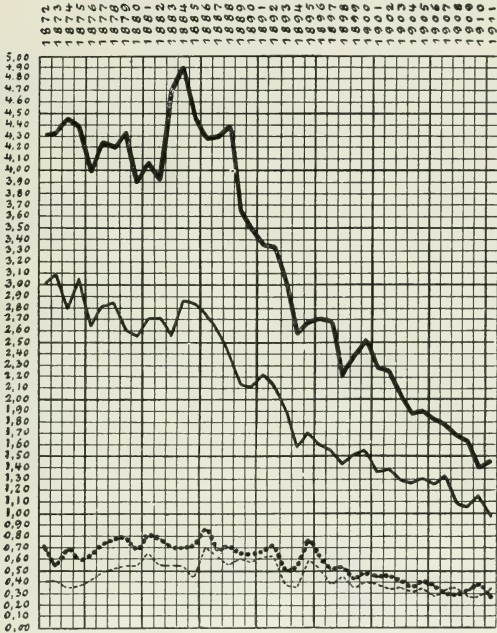
— Sterblichkeit an Lungenschwindsucht auf je 1000 (m)

— " " " " " 1000 (w)

●●●●● " " {Tuberculose an-} " " 1000 (m)

----- " " {derer Organe} " " 1000 (w)

in der Stadt Hamburg 1872 - 1911.

TABLE IX.—Showing the reduction in mortality is not due to growth of the city, but to the increase of inherent powers of the inhabitants.

He maintains that the later the infection occurs the less is the liability for clinical manifestations and believes they are seldom seen in children infected after the fourth year. Whether this is due to a previous light infection or is caused as a physiological result of increased resistance he does not state. At any rate, these observations teach we must recognize an immunity of the growing organism toward outside infection. They also make very improbable the view that consumption in the adult is the result of exogenous infection and support the contention that the infection of early years causes the tuberculous habitus, and therefore will be the cause of the later phthisis.

Roemer accepts the views of Pottenger and Pollak, but still maintains that the physical habitus can arise independent of tuberculosis; in his opinion he is supported by many observers. Roemer believes observations should be made to ascertain if men clinically considered non-tuberculous, but with typical paralytic chests, will remain negative to sensitive tuberculin tests (the stick method).

Conditions may be defined as follows:

If tuberculous infection does not cause rapid death it leads to increased resistance against a tuberculous infection.

The resistance so caused is potent in preventing outside infection in later years.

Particular conditions of a physical or pathologic kind due to the incorporation in the body of the tubercle bacilli are such that the degree of immunity is not sufficient to prevent a metastatic reinfection. Thus it occurs that a new focus develops with renewed manifestations of tuberculosis.

Experience teaches us to view these as metastases caused by a relatively severe infection in childhood.

A particularly disposed local condition for the origination of this second condition is perhaps in evidence.

From epidemiological reasons Hillenberg opposes these views. In his investigations on the spread of tuberculosis in a neighborhood with but slight saturation with tuberculosis he found a not insignificant number of children infected. He therefore concludes that the elders of these children in their youth must have been proportionately infected, and thinks it strange that in spite of this so few or none in later life became consumptives, although when children they were infected with latent tuberculosis.

Roemer directly opposes this view and insists that the large majority of infections in children do not result in consumption in later life and are never noticeable except by the insensible protective influence against further infection; he further insists that in those cases in which consumption appears later a particularly severe early infection occurs. In the territory investigated by Hillenberg he thinks there was no indication of serious early infections, and the failure from consumption of those only lightly infected in childhood is not a contradiction of his views, but a support of their correctness.

Ranke has recently devised a very interesting chart that shows the death

rate from the recognized forms of the tuberculosis of children and adults. The one being characterized by acute general tuberculosis, the other by chronic phthisis. These forms are seen in two curves. We believe the formula correct which states "that phthisis is an after-disease of generalized tuberculosis."

The increase of mortality from the sixteenth year on can be caused theoretically by increased facilities for infection; practically this in the highest degree impossible, for phthisis does not immediately follow an opportunity for infection, but very frequently appears to arise spontaneously after inner or outer general or local injuries.

Ranke shows that the phthisis of adults is the result of the changes inaugurated by a previous infection. For further proof he indicates the rarity with which consumptives have the trachea, mouth, fingers, nose and eyes involved, notwithstanding daily opportunities for infection. He mentions
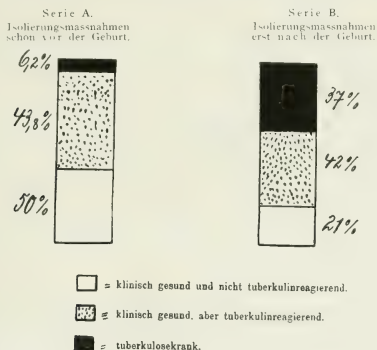
TABLE X.—Diagram showing the relative merit of protective measures taken before and after the birth of the child.

again the rarity of hemostatic metastases in phthisis in comparison with their frequency in general tuberculosis, although it is proven that in phthisis the tubercle baccilli are frequently found in the circulation.

Ranke proves further that when secondary infections occur they are of the type of superinfections and due to a saturation of the blood with bacilli when the resistance is low.

In the efforts to combat the spread of tuberculosis it must be attacked from a new viewpoint.

It is shown by the practical consequences that in the fight against the tuberculosis we must either prevent the severer forms of infection, which are

ultimate cause of the varities of tuberculosis found in adult life, or we must prevent the ominous metastases in individuals infected in infancy. It is self-evident that only the assault of both positions can be efficacious. Because of the fact that tuberculosis is a result of infection early in life, Roemer is not an ardent advocate of the advocacy of a personal hygiene that endeavors to inaugurate an effectual antagonism in adults. He believes this practice contrary to natural processes as is shown by experiments in animals.

In eliminating cattle tuberculosis no hygienic rules are efficient; only methods that prevent infection show positive results.

The complete inefficiency of the hygienic method can not be better illustrated than by the facts established by the veterinary service in the Hessian district where, notwithstanding extensive efforts to prevent tuberculous saturation the loss in the majority of instances was very considerable, while the lamentably appearing dark stalls of the small farmer were almost tuberculosis free.

In the pampas region of Argentina the spread of tuberculosis among cattle was unopposed, although they were living under the most favorable conditions in the open air in a sunny climate, until the owners concluded to exclude English breed cattle.

As long as there is a source of infection open-air conditions are useless, and when calves are fed infected milk, as is done in many parts of Europe, the attempt to make general hygienic measures efficient is useless. While isolation of consumptives is a relative isolation it is in line with the prevention of infection.

The efforts to cure tuberculous children by means of open-air schools and nourishing food, by means of sanatoria and isolation homes, is a duty. Of all measures of prevention the protection of the child is the principal one. This does not exclude other methods.

The effort must be made to prevent severe childhood infection. If it is known in what families tuberculosis is present a great advance will be made. This may be ascertained by the Pirquet method. If the children can then be protected a great problem will be solved. By following out this method Effler has already attempted to judge the efficacy of this plan. While his results are few they are remarkable. With sixteen children born and brought up in families in which before their birth proper methods were counseled there were at the time of the investigation eight well and not responsive to tuberculin; seven clinically well but reacting; one had pronounced tuberculosis. This child was from parents with open tuberculosis, and, because of this, the measures of prevention could not be thorough.

Of nineteen children in which measures of precaution were taken after birth in open tuberculous families, four were healthy and non-reacting; eight healthy, but reacting; five were tuberculous. These figures are small, but very suggestive, and indicate what is necessary. We know how to protect the children; we possess means to control the disease; we must now use them.

It is first necessary to be convinced that the secret of the origin of consumption lies in early life, which then becomes the field for strenuous effort.

The opportunity to establish the truth of these investigations lies in the field of the family physician. Upon him alone will rest the responsibility for results. In the accomplishment of this duty he will be supported when necessary by the strong and persuading influence of the health department and such other organizations as earnestly labor for the eradication of the tuberculosis scourge.

DIZZINESS.

M. F. McCarthy, M. D.,

Cincinnati

Until comparatively recently we have not had at our command the means to study and classify the causes of dizziness. Until the last decade our understanding of the mechanism controlling balance, the disturbances of which could result in dizziness, was very hazy, being made of the uncorrelated efforts of laboratory workers whose deductions were made for the most part from animal experimentation.

In 1825 Flourens made excisions of portions of the labyrinths of animals and noted that this caused movements of the eyes and definite disturbances of equilibrium. Purkinje at the same time made experimental studies in turning human beings and made observations on the resulting nystagmus and vertigo. In 1861 Meniere published his now famous case history of Labyrinthine Haemorrhage, verified by post-mortem examinations, and by his accurate observations established the syndrome known to be typical of the so-called "Meniere's Disease." Ewald and Hoegyes, after years of patient endeavor and research, were able to state some of the basic laws of labyrinthine physiology. From the observations of these two men, together with the added experience of other investigators, Robert Barany was able to draw the material for his magnificent work which has brought labyrinthine studies out of what was entirely impractical state and into the practice of the clinics. His most notable contribution was made in 1913 and since that time many observations, verified by autopsy, have brought this work to a degree of refinement in method not hitherto known.

Contributions from time to time by workers in this country, most notably perhaps Jones and Fisher, of Philadelphia, have brought us to the realization that there is some clinical value to these tests.

The text-book of Jones and Fisher, "Equilibrium and Vertigo," has been helpful in that it has stimulated interest in labyrinthine studies, but has gone far toward bringing all labyrinthine studies into question by the wide and sweeping generalizations therein contained. The work of Griffith, carried on and published from the psychological laboratories of the University of Illinois has brought much of the work done by Jones and Fisher, as well as the other workers associated with the Aviation Service during the war, into question.

In as much as the study of dizziness is largely a study of the mechanism which controls body balance, any discussion of this subject must be largely of a physiological nature. It is the study of a new special sense which must be added to our study of the special senses of hearing, taste, touch, smell, sight and muscle sense. This new sense we must call the kinetic-static sense, or the sense that appreciates head motion and head position, and which thus in a sense appreciates body motion and body position. This sense has as its

end organs the labyrinthine portions of the internal ear, and these end organs have as their sole function an important role in the maintenance of balance. The term "end organ" is used for the very special purpose of emphasizing the fact that the internal ear is an end organ and nothing more and that any study of the disturbances of balance must take into consideration not only the end organ but the nerve pathways by which its messages reach the central nervous system. Also it must deal with the method of the distribution of these messages and their attendant reactions, so far as they are known.

Perfect equilibrium is maintained by the correlated activities of the special senses of sight, muscle sense and the kinetic-static sense. Vertigo can be caused by disturbances of vision and by a loss of the proper ocular muscle balance. This type of vertigo is ordinarily set right at once by properly fitted glasses and can be recognized by the fact that it is not present when the eyes are closed. Muscle sense when decreased, absent or perverted may decidedly interfere with equilibrium but does not cause dizziness. By far the largest number of those complaining of the most disturbing symptom of dizziness are those who have sustained some loss of or irritation to the kinetic-static sense either in its end organs, the labyrinths, or to some portion of their nerve pathways.

As physicians we are too often given to loosely considering the ear as an organ such as the heart or the liver, forgetting that the ear is only the end organ of two very complex nerve pathway systems, the one having to do with the acoustic function and the other making possible the knowledge of the position and motion of the head. In as much as these two sets of fibers travel in the same nerve sheath as far as the point where they enter the medulla, the tests of hearing are of considerable value in giving some idea of the state of the eighth nerve at least as far as the point where it enters the medulla. For many years the hearing tests were the only means by which the condition of the vestibular fibers might be ascertained, it being reasoned, with some foundation, that any condition affecting one set of fibers, in the same nerve, should affect all the other fibers in that nerve.

The difficulty here encountered is that later observation has taught that this is only partially true. For some reason not entirely comprehended, the fibers having to do with hearing are much more sensitive to the actions of toxins and much less hardy when subjected to pressure or like injury. Under such conditions the first fibers to cease to function are the acoustic fibers, and often we have tested cases in which the acoustic function has been completely lost but in which the vestibular fibers were still functioning. The explanation offered for this phenomenon is that in the scale of animal development the last functions to be acquired are the least hardy and resistant to attack, the sense of hearing being acquired long after the kinetic-static sense. However, the tests of hearing do turn some light upon the state of the vestibular fibers, but, what to most of us is more important, is

that tests of the vestibular fibers give us an insight into the condition of the acoustic fibers.

If we are to search for the causes of dizziness then we must inquire into the state, first, of the labyrinthine portions of the inner ears, and second, their respective nerve pathways. So we are brought directly to an inquiry into the function of the labyrinthine portions of the inner ear. Just as the child's first vision is upside down and the higher brain centers learn to interpret the inverted image, so when the first head movement occurs and the endolymph of the semi-circular canal moves, the higher centers of the brain learn to associate that endolymph movement in one direction as indicative of head motion in the opposite direction. So, too, when the head is rapidly turned from one side to the other, the higher centers in an effort to stabilize the sensorium, make the eyes lag behind a little during the turn and cling to the objects as they pass. This lagging behind is the slow component of nystagmus. As the eyes give us some new object to which they are clinging during the turn, they are brought up with a sharp snap to seek some new object and this is the rapid component of nystagmus. This explanation, as offered by Jones, seems somewhat plausible, and whatever explanation we desire to accept we do know that movement of the endolymph in one direction in the semi-circular canals has become associated with a slow eye movement in the same direction and a rapid eye movement in the opposite direction, the slow eye movement being the direct result of stimulation from the semi-circular canals. That the higher centers, most probably in the cerebral cortex, are responsible for the rapid component of nystagmus seems to be borne out by the fact that the rapid component is not present in induced general anaesthesia or in destructive lesions of the cerebral cortex. Vestibular irritation, under such conditions, results in eye movement in the same direction as the endolymph movement, but the rapid component fails to materialize and the eyes are deviated in this direction as long as the vestibular irritation lasts—conjugate deviation.

Long years of experimental work on the labyrinths and gradual accumulation of clinical evidence has brought us to the almost certain understanding that it is through constant messages through the semi-circular canals that balance of the body is ordinarily maintained, for it is thus that the higher centers realize head position and head movement.

Since balance is in a large measure dependent upon this knowledge of head position and head movement, anything that disturbs the mechanism which makes this knowledge possible, disturbs the sense of balance or the kinetic-static sense and dizziness results. Then, too, we have come to know that the labyrinths are constantly sending messages to the nuclei controlling the eyes muscles and maintaining for the eye muscles a sort of tone or balance. We know this to be true as any irritation to or cessation of function of either labyrinth immediately results in nystagmus, which has a definite direction and type varying with the labyrinth affected. For example: Injury or irritation to the right labyrinth results in a slow movement of the

eyes to the right and a rapid eye movement to the left, this being known as nystagmus to the left and vice versa.

Knowing that loss of function of a labyrinth or irritation to it or its associated pathways is accompanied by dizziness or nystagmus, or both, by the analysis of these two symptoms we have a method of arriving at some conclusion concerning the cause and its location. In the analysis of dizziness one must consider the direction and intensity of it as manifested by the so-called act of past pointing. When the eyes are closed and one is having the subjective sensation of turning, if the finger is put upon an object and then lifted into the air, when the finger is brought down to find the object again, instead of finding it the finger points past it to the right or left, depending upon the direction of the subjective sensation of turning. If one feels that he is turning from right to left he feels that after having once touched an object and raised his finger from it, that the object has moved past him to the right, and so when he again attempts to find it with his eyes closed, he points past it to the right, or, as it has come to be termed, past points to the right. Bimanual past pointing as measured in inches gives some indication as to the intensity and direction of the vertigo. Since the vertigo has resulted from some irritation to or destruction of the labyrinths or their pathways, past pointing gives some insight into the state of these end organs and their fibers, as well as throwing some light upon the nature of the stimulus or lesion and its possible location.

Past pointing in itself is only a small aid to diagnosis and to this observation must be added other observations before even a conjecture is warranted. Past pointing is probably less important as an observation than the analysis of nystagmus, for the absence of nystagmus after labyrinthine irritation is always pathological, whereas the absence of past pointing may indicate a pathological condition or it may not. However, presence of past pointing in both directions with both hands, elicited by the use of the caloric tests, is strong evidence that the cerebellar hemispheres are intact and such an observation certainly has its value.

It is not the purpose of this paper to attempt to cover the more detailed portions of the analysis of labyrinthine responses to stimulation. Rather it is the purpose to discuss the basic principles of the tests of labyrinthine function as brought out by the efforts of many workers since interest first began in this question.

With the head at thirty degrees forward, the plane of the horizontal semi-circular canals is parallel with the floor, and when the body is rotated with the head in that position, it is claimed that only endolymph movement is in the horizontal canals. Therefore, we know that any resultant response given in the form of nystagmus or past pointing must come from the endolymph movement in the horizontal canals. The greatest objection to the turning tests is that both labyrinths are stimulated at the same time. If the lesion should be unilateral and not complete, the value of the turning tests is almost nothing. For reliable diagnostic purposes there is only one set of tests of real

value and these are the so-called caloric tests, in which one ear at a time is douched with water cooled to sixty-eight degrees Fahrenheit. By this method, by altering the position of the head, each set of canals can be tested separately and each variation in the normal responses, in intensity, direction and duration of nystagmus and the amount and direction of past pointing be observed and recorded.

With the head at thirty degrees forward, the horizontal canals are parallel with the plane of the floor, and the plane of action of the vertical canals is at right angles to the floor plane. When water at a temperature of sixty-eight degrees Fahrenheit is run into an external auditory meatus, with the head in this position, the bone immediately adjacent to the labyrinth is chilled and the specific gravity of the endolymph, rising at the chilled point, a current is started downward toward the ampulla in the vertical canals only. The fluid in the horizontal canal remains unmoved as it is parallel with the plane of the floor and no force of gravity is in action on its endolymph. By varying the position of the head from thirty degrees forward to sixty degrees backward, we place the plane of action of the vertical canals parallel with the floor and now the horizontal canals are at right angles to the floor plane. At once the endolymph of the vertical canals comes to rest and the current, if it is such, begins to move downward away from the ampulla in the horizontal canal. By this means we are able to test each set of canals separately without having to resort to head motion to set up our endolymph currents, the same responses being given in past pointing and nystagmus as though head motion had occurred in a direction opposite to the direction of the endolypmh current or flow. While variations do occur in cases where, due to drum thickening or bone changes, the chilling of the canals is delayed, the average patient, following douching of an ear with water at a temperature of sixty-eight degrees Fahrenheit, will exhibit the ocular movements characteristic of nystagmus in from forty to sixty seconds from the time the douching is begun. Forty seconds was the time as set by Jones in his review of many thousand tests made on aviators during the war. However, our tests on the average clinical patient have shown that this figure is a little low and that it is more apt to be fifty to sixty than it is forty, and often may run over, that in cases that do not exhibit any marked drum changes. Some of these patients have been douched several times with the same results and have been followed for over a year without exhibiting the slightest suggestion of any pathological changes in either the acoustic function or the kinetic-static sense. However, the thousands of tests being done and to be done in the future will settle such questions very definitely within the next decade.

If the douching of an ear is continued until the ocular movements reach a maximum, there should be present past pointing with both hands in the same direction to the side of the ear stimulated. This past pointing may vary somewhat in amount, the reaction being somewhat more marked in some people. Since this past pointing is in a sense an indication of the

amount of dizziness, we ordinarily expect it to be present in continuous and well-defined vertigo. Providing there is not some lesion of the lobes of the cerebellum which will interfere with the synergy of the arms as the effort is made which results in inward or outward pointing of the arms, this past pointing should be bilateral.

When we remember that in the caloric tests, done by douching the ears, we are testing each set of canals separately, as well as their associated nerve pathways, the significance of the tests becomes apparent. In the last few years it has become fairly well established that the fibers from the vertical and horizontal canals do not follow the same paths after the fibers of the eighth nerve have entered the upper portion of the medulla. The paths they pursue, as at present understood and upon which understanding successful localizations are being made, is that the fibers from the horizontal canals dip down into the medulla and end in Dieter's nuclei. From there, fibers pass to the posterior ground bundles which join up the nuclei of the nerves controlling the eye movements exhibited during nystagmus. The greater part of the remaining fibers pass into the inferior cerebellar peduncles of their respective sides and so reach the cerebellar nuclei.

On the other hand, immediately upon entering the upper portion of the medulla, the fibers from the vertical canals pass upward and enter the pons, where they terminate in some homolateral nuclei as yet not certainly known. These nuclei are also linked up to the pontine nuclei controlling the eye movements, by fibers which pass to the posterior ground bundles. The greater part of the remaining fibers reach the cerebellar nuclei by way of the middle cerebellar peduncles of the same side.

Hence, it is said by testing the horizontal canals we are testing not only the integrity of the canals themselves, but the integrity of the upper portion of the medulla, the inferior cerebellar peduncles, and the homolateral cerebellar nuclei. So, too, by testing the vertical canals of one side, we test also the integrity of the lower and lower middle portions of the pons, the middle cerebellar peduncle and the cerebellar nuclei of the same side. Since it is by means of the superior cerebellar peduncles that the cerebellar nuclei are joined to the higher centers in the cerebral cortex, where take place the complex associations of stimuli necessary for the knowledge of motion of the head or of its position in space, we are given some information concerning the state of the tracts of the superior cerebellar peduncles themselves. Since with our tests we are given some information concerning the activities of the fibers traversing such important structures as the medulla, pons, the cerebellar peduncles and hemispheres, as well as the higher cerebral centers from which originate the arm movements having to do with past pointing, their importance warrants consideration. Nor is this importance lessened by the fact that in some measure the condition of each of these structures can be estimated separately.

Our interest in this work has come not from any desire to enter upon a career in neuro-otology, but rather from a desire to find some means of

throwing light upon the condition of the internal ears in all too numerous cases of hopeless deafness that have come into our hands. Then, too, we have been seeing more and more patients complaining of dizziness in which we felt the integrity of the internal ears was established. Since no examination of the internal ear can be complete without having considered the state of its nerve tracts as well, there is no choice for the otologist who is confronted with the necessity of attempting to find the cause or causes or recurrent dizziness in one of his patients. All the light that neurologists, with whose collaboration this work should always be done, can throw together with that of otological observation, is only too often too feeble to allow us to see clearly to the cause and so be guided to the relief of the suffering patient.

There is no doubt that most of the cases of dizziness which we see are due to affection of the internal ears or their immediately adjacent nerve supply. The difficulty may be occasioned by some disturbance of the blood supply to the parts, anaemia or hyperaemia, or to the presence of some toxic material which has reached these structures either through the blood or lymph chanels or by the simple diffusion or toxic material through the bone, as can happen in purulent infection of the middle ear. These cases, once the toxic material is eliminated or the circulatory disturbances set right or the middle ear drained of the pus, promptly recover. However, we must be constantly on our guard for the cases of persistent dizziness or for those cases which recur at frequent intervals and in which there is some question as to whether means taken to combat the cause is being effective or not. We must not forget that it may not have been our remedial measures which resulted in the cessation of dizziness, but that it may simply mean a cessation in the amount of local or general nerve pressure. Nothing is more perplexing than, in cases of known central lesion accompanied by a rise of intracranial pressure, to find that one day a set of fibers are working and the next day to find their function totally lost, to be in turn followed by almost complete recovery of function within the following twenty-four hours. Intracranial pressure as manifested by inhibition of nerve action is certainly an extremely variable quantity and marked and prolonged remissions of symptoms are often found in even the most serious of intracranial lesions. It is these remissions which lull us so often into a false sense of security in the early observation of patients complaining of dizziness and the patient is dismissed from observation as having been the victim of some unknown type of toxaemia which has passed away.

We must remember that dizziness can result from any disturbance to function of the semi-circular canals or of their nerve pathways to the cerebral cortex. The stomach itself is not the cause of dizziness except as a hyperacidity may influence the quantity or quality of the blood supplied to these parts. Focal infection from teeth or tonsils, constipation, diabetes, nephritis, tumor masses, and so forth, only cause dizziness as they destroy parts of or upset the workings of these balance control systems.

Every disturbance of these systems is immediately attended by dizziness or nystagmus, or both. If complete destruction of one of these balance control systems has taken place, as may occur in the destruction of the internal ear of one side or the complete degeneration of an eighth nerve, this dizziness may persist in the most severe form for weeks, attended by an almost constant nystagmus of a type that varies in its nature according to the ear or nerve affected.

Gradually, in this form of disturbance to the kinetic-static sense, the remaining system takes up in part the function of the one lost and the higher centers learn either to ignore the disturbing stimuli coming in over nerve pathways from the destroyed area or to rely upon the remaining system reenforced by the knowledge of the body's position in space by the muscle and visual senses. The past pointing and nystagmus present in such disturbances, resulting as they do from some stimulus or lack of stimulus from within, are termed spontaneous past pointing and spontaneous nystagmus to differentiate this type from that resulting from external stimuli, such as are used in the caloric and turning tests.

There are two types of spontaneous nystagmus to be observed—the rhythmic, in which it is possible to distinguish a slow movement in one direction associated with a rapid movement in the opposite, and the oscillating type, in which both movements are of equal rapidity. The oscillating type has no relationship whatever with the disturbances of the kinetic-static sense, and is due entirely to either an early acquired or congenital central visual defect. This type of nystagmus becomes much more marked whenever visual fixation is attempted and can be differentiated with relative ease from the rhythmic. Close observation of the rhythmic type will disclose to which side the rapid movement or component is taking place, and if, for example, it is to the right, then the nystagmus is said to be to the right. Rhythmic nystagmus resulting from the complete cessation of function of one or the other of the balance control systems, has a mixed rotary and horizontal movement to the slow component. When it results from a disturbance to the vertical canals or their nerve supply alone, the nystagmus has a rotary element alone as its slow component. When, however, the disturbance affects the horizontal canals or their related nerve supply, the slow component is entirely horizontal. So it is that the analysis of spontaneous rhythmic nystagmus gives us often very important clues as to the type and location of the disturbance in function that is resulting in dizziness to the patient. Spontaneous rhythmic nystagmus upward or downward is practically always indicative of pontine pressure.

The difficulties attending constructive work in this field are manifold. Cases of this type progress so slowly that many observations made on those who are in the early stage of the development of their lesions are never followed by later observations. In a semi-invalid state they drift from one physician to another and often are completely lost for the opportunity of further study. This work is still in the active phase of discovery and prog-

ress and much will be added in the future which will be of great benefit to humanity. I have no desire to paint the picture in too glowing terms, for the diagnosis of many of these conditions is a matter of prolonged and painstaking observation. In many, many cases we fail to make a diagnosis due to obstacles which we have not yet been able to overcome. There is no doubt that the tests have been overrated by some over-enthusiastic workers who, in a measure, have brought the tests into a certain amount of disrepute. There is no doubt, however, that this work has its very positive field of usefulness and that the future will see much added in the improvement of technique and a widening of its breadth of service.

I wish to take this opportunity to thank Dr. Louis Fisher, of Philadelphia, for his kindness in allowing me the privilege of reviewing his case records. I wish also to express my appreciation for the kindness of Dr. Bentley and Dr. Coleman Griffith, of the Psychological Department of the University of Illinois. I wish to express my admiration for the accurate and monumental work being carried on in their laboratories for the purpose of advancing our knowledge of labyrinthine physiology.

THE PINEAL GLAND.*

THE PINEAL GLAND'S INFLUENCE UPON GROWTH AND DIFFERENTIA-
TION WITH PARTICULAR REFERENCE TO ITS INFLUENCE
UPON PRENATAL DEVELOPMENT.

CAREY PRATT McCORD, M. D.,

Detroit.

I. INTRODUCTION

(A cursory review of recent work pertinent to pineal functioning.)

The evidences that link the pineal body with a glandular function are
much less definite than for such glandular organs as the thyroid, hypo-
physis, ovary, and the suprarenals. Doubt is frequently expressed that the
pineal body is more than a functionless vestige of what was once, in earlier
evolutional stages, a functioning eye. Other observations have led to the
contention that the pineal, through metamorphosis, has become a highly spe-
cialized tissue that serves the body in a manner comparable with the major
members of the endocrinous system.

The purpose of the present paper is to group the essential findings from
the recent literature into a concise, unbiased résumé, adequately expressing
the status of the pineal body as a functioning organ. To this are added the
writer's more recent observations upon the growth of young animals under
the influence of pineal materials.

ANATOMY AND EMBRYOLOGY
(Bibliography numbers 1-57)

The pineal body (pineal gland, epiphysis, conarium) is situated in the
brain just beneath the splenium of the corpus callosum. (Fig. 1.) It lies
suspended between the anterior quadrigeminate bodies. The gland is con-
sequently just above the Sylvian aqueduct. The internal cerebral veins lie
above and partially encircle the pineal. In the human the pineal is nearly
trilateral in shape, in sheep is round, in cattle is oval. The average weight in
cattle is .2 grams and in sheep .13 grams. Primarily the pineal is developed
as a thin ependymal diverticulum from the diencephalon, extending between
the posterior and habenular commissures. At a later stage this diverticulum
thickens and encloses some of the adjacent vascular mesoderm to form the
mature organ. (Streeter.)

In those publications cited in the bibliography as pertinent to the anat-
omy, embryology, and histology of the pineal, the studies have, for the most
part, been prosecuted toward establishing (1) the presence of glandular
tissue; (2) the presence of contractile tissue supporting the view that the
gland is a valve regulating the flow of cerebrospinal fluid; (3) nerve fiber
communication between this gland and other parts of the brain; (4) evi-
dence of involution changes in the gland indicating a cessation of function.

These publications may be summarized as indicating: (1) Complete cytologic studies in several species allow the inference that the pineal body is glandular in nature. The glandular elements, however, are few and illy defined. (2) The occasionally demonstrated muscle fibers in the pineal are without significance to pineal function. (3) Nerve fibers and neuroglia are to be found at least in certain animals, but these are probably of trivial import. (4) The gland undergoes involution changes, beginning in the human as early as the seventh year. Involution is pronounced at puberty. The degeneration is, however, not complete and the histologic picture of the adult gland is not such as to remove the possibility of a continued function in adult life.

PINEAL NEOPLASMS AND RESULTING FUNCTIONAL DISTURBANCES
(Bibliography numbers 100-189)

Tumors of the pineal are not of frequent occurrence. The total number of authentic cases, with subsequent necropsy findings in some, is not more than seventy. These cases have been the source of the greatest information as to the functions of the pineal. In 1898, Heubner described a boy of four and one-half years who showed a precocious sexual and somatic growth. The body of this boy was that of a boy of eight or nine years. The genitalia corresponded to the proportions found at puberty. The pubic hair was 1 cm. long. A year later at autopsy a teratoma of the pineal was demonstrated. By 1907, Marburg was able to collect forty histories of such types. He sought to establish a clinical entity for pineal dysfunction. The term "Macrogenitosomia præcox" has subsequently designated this condition. In a more recent paper, Marburg attributes to the condition the following characteristics:

1. General. These include all the usual signs of intracranial pressure, usually secondary to a subsequent internal hydrocephalus.

2. Neighborhood. These for the most part are dependent upon encroachment upon the quadrigeminate bodies, leading to diverse oculomotor paralyses and pupillary disturbances, and encroachment upon the cerebellum, with ataxic manifestations.

3. Constitutional. Under this designation are grouped the manifestations attributable to the derangement of the pineal glandular function. This constitutional syndrome consists of first, early sexual maturity, evidenced in the enlarged sex organs, pubic hair, general body hair, early change in voice; second, precocious mental development, evidenced in the maturity of thought and speech; third, general body overgrowth to the extent that a child of five or six years may have the appearance of a child of eleven or twelve.

Frankl-Hochwart similarly has summed up the characteristics of this pathologic state. He states, "When one finds in a very young individual, along with the general symptoms of tumor as well as the signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of

hair, adiposity, somnolence, premature genital and sexual development, and finally intellectual maturity, one must think of pineal tumor."

Of the seventy cases at the present time available in the literature, only twenty-five occurred prior to puberty. Because of the pineal involution that occurs by the time of puberty, only in these twenty-five cases are constitutional manifestations to be anticipated. It is significant that with two exceptions all cases occurred in boys.

Many cases of pineal tumors before puberty manifest none of the signs of precocity of development that are so striking in a few selected cases. A study of the clinical material reveals how little consideration has been given to the possibility of pluriglandular involvement. In fact, some early cases
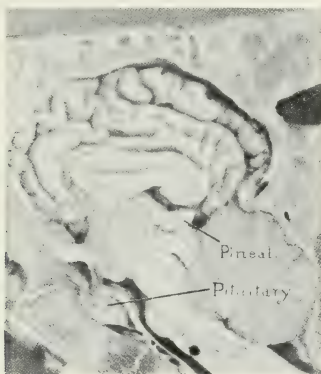
Fig. 1—Sagittal section of beef brain, showing size, position, and relation of pineal gland.

the necropsy demonstration of a pineal tumor led to the association of all prior metabolic changes to pineal functional perversion. This grew out of the prevalent conception of each endocrine gland as an entity entering into no interrelations with other similar organs. Judging these cases in the light of recent advances in pituitary pathology and physiology, it is difficult to delineate the manifestations of pure pineal derangement from a pluriglandular condition. Cushing has pointed out that from the intracranial alterations attending pineal neoplasms, the hypophyseal functions are readily deflected from the normal.

This infrequent condition in which the growth and differentiation into the adult is so deviated from the normal that very young children acquire

in part the sexual, mental and somatic characteristics of maturity, has naturally led to diverse attempts to induce such a condition experimentally. Through the extirpation of the pineal, through the feeding of pineal substances to young animals, through the intravenous and subcutaneous administrations of pineal extracts, has information been sought as to the significance of this organ in the body's economy. The outcome of such investigations are described in subsequent paragraphs.

EXTIRPATION OF THE PINEAL GLAND
(Bibliography numbers 71-78)

Situated near the center of the brain, the inaccessibility of the pineal has prevented any widespread use of this method. The trauma is necessarily severe and until the recent reports by Dandy (1915) and Horrax (1916) the mortality has been very high—seventy-five deaths out of ninety-five operations in one series, and twelve deaths out of fifteen operations in another. With so high a mortality it may be questioned whether the few survivors would exhibit constant changes referable to pineal deprivation. The mortality is usually due to hemorrhage into the ventricle from injury to the central cerebral veins, or to direct injury to the quadrigeminate bodies or adjacent brain tissues. Dandy has recently developed an operative procedure whereby much of the trauma is obviated. The essential innovation lies in an approach through section of the splenium of the corpus callosum thus permitting freer manipulations in the operating field. Although the mortality may thus be reduced, the results obtained by Dandy, on comparison with those obtained more recently by Horrax, are uniformly dissimilar. The respective summaries of these two investigators quoted below indicate how incomplete are our available data bearing upon extirpation as a method of approach to the problems of pineal function. Dandy states:

"1. Following the removal of the pineal I have observed no sexual precocity or indolence, no adiposity or emaciation, no somatic or mental precocity or retardation.

"2. Our experiments seem to yield nothing to sustain the view that the pineal gland has any active endocrine function of importance either in the very young or adult dogs.

"3. The pineal is apparently not essential to life and seems to have no influence upon the animal's well-being."

These negative findings are in keeping with the earlier work of Exner and Boese, and Biedl. Subsequent to Dandy's publication an extended report has been made by Horrax, whose positive findings are in keeping with those of Foa and Sarteschi. Horrax states:

"1. Total experimental pinealectomy is possible in guinea-pigs and rats.

"2. Pinealectomized made guinea-pigs show a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of the testes and seminal vesicles, over control pigs of the same litter.

"3. Histologically the testes and seminal vesicles of these animals, if taken before the age of sexual maturity, show a more advanced physiological state than their controls.

"4. The pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight.

"5. For several reasons, young rats are likely to prove better subjects for experimental pinealectomy than young guinea-pigs, and some evidence of hastened maturity has been obtained in this species."

IMMEDIATE RESULTS FOLLOWING THE INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION OF PINEAL EXTRACTS
(Bibliography numbers 58-70)

Unlike the intense cardio-vascular action of suprarenal extracts, or the uterine contracting action of pituitary extracts, the immediate results from intravenous or hypodermic injections of pineal extracts are not pronounced.
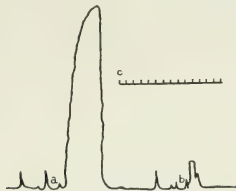
Fig. 2.—A comparison of the effect on surviving guinea-pig uterus of pituitary and pineal-gland extracts. The height of contraction from the pineal extract administered at *B* is trivial in comparison with the contraction at *A* induced by the much smaller quantity of pituitary extract. Time in minutes.

Such phenomena as decrease in arterial tension, dilatation of the blood vessels, altered amplitude and rate of the heart beat, diuresis, glycosuria, and uterine contractions have been reported and confirmed. Under experimental conditions the contraction produced in the uterus by 1 cc. of 20 per cent. pineal extract is much less intense than the contraction produced by 1/200 cc. of 20 per cent. pituitary extract. (Fig. 2.) The intensity of these several activities is so slight that at the present time only technical importance may be attached to these findings.

FEEDING EXPERIMENTS WITH PINEAL GLANDS
(Bibliography numbers 79-87)

The syndrome of precocious development seen in the human is usually interpreted as the outgrowth of pineal deficiency—a hypopinealism. Such being the case, if the feeding of pineal materials determined any changes, a state just opposite that cited above would be anticipated—a condition of deferred sexual, mental and somatic maturity. Curious to record, feeding experiments lead to rapid sexual and somatic development.

Dana and Berkeley fed pineal materials to young animals (kittens, rabbits, guinea-pigs), and noted a 25 per cent. excess in weight over controls. These investigators sought to determine the extent of stimulating influence upon children of low mentality. Fifty feeble-minded children were treated and suitably controlled with other children of the same age and diagnosis. Binet tests were the criteria of mental advancement. No physical changes resulted but on prolonged treatment the mental development was greater than that prior to treatment and in excess of control children of the same

mental age. These studies on feeble-minded children afford certain technical evidences of value but the quantity of improvement resulting is not sufficient to warrant any widespread use of pineal materials as a profitable treatment of feeble-mindedness.

Hoskins (1916) in feeding experiments upon albino rats, studied the influence upon the growth of the various ductless glands including thyroid, thymus, hypophysis, and pineal. His results would indicate that none of these glands have any constant effect upon the growth-rate of young rats.

McCord (1914, 1915) employed 400 young animals (chickens, guinea-pigs, dogs) in experiments to establish the extent of influence the pineal exerts upon growth and development. He concludes from his experiments that the same precocity of development usually attributed to pineal deficiency (hypopinealism) was obtained in animals by supplying an increased amount of pineal substance by feeding or injecting pineal preparations. Such administration of pineal substances led to a more rapid growth of body than normal, and determined an early sexual maturity. The excess in rate of growth was most pronounced (40.9 per cent. excess in eleven weeks) in young animals fed with pineal tissue obtained from young animals. No tendency to gigantism has followed pineal administration. After maximum size was attained, pineal administration appeared to be ineffective. Both males and females respond to the influence of pineal substances in rate of growth, but the response has been more definitely manifested in males.

II. THE PINEAL GLAND'S INFLUENCE UPON GROWTH AND DIFFERENTIATION

(A record of experiments upon postnatal and embryonic growth-differentiation processes)

In the developmental processes inaugurated at conception two distinct phases are to be observed—growth and differentiation. In intra-uterine life differentiation into specific organs and tissues is the essential process. In pre-adult life, growth processes are dominant. At puberty differentiation again asserts its influence. In adult years both these developmental processes are less in evidence, a condition we commonly designated as maturity.

These two phases of development are necessarily intricately interrelated, but within certain limitations may be separately altered. Traces of thyroid tissue added to the water in which tadpoles live will bring about the complete transformation of the tadpole into a miniature frog within one week, whereas normally this metamorphosis consumes from four to six months. (Gudernatch.) This phenomenon is due to the intense differentiative action of the thyroid. Similarly thymus tissue retards differentiation of tadpoles. At the period of development wherein normally tadpoles begin to differentiate, thymus fed tadpoles continue to grow larger without differentiation. Manifestly both these factors in development are ultimately dependent upon the quantity or quality of cell activity.

In our earlier records of the influence exerted by the pineal upon development we employed young animals and chicks. Variations were introduced to reduce the possibility of incidental error in dosage, in method of administration, in source of materials, in age of the test animals. With the exception of two series we have uniformly found that young animals who had been fed (or injected) pineal materials have outgrown their controls of the same age. (Fig. 3.) In one series the difference was 40 per cent. at eleven weeks of age. No tendency to gigantism was observed. As the normal adult size was approached the stimulative action of the pineal was no longer effective. The testes of certain of these rapidly developed guinea

pigs were examined in comparison with controls. Grossly the testes from pineal fed animals were 50 per cent. larger. Microscopically the cellular elements were far in advance of controls and were characterized by very active spermatogenesis. The females gave birth to young when the controls were in the middle third of their gestation. At first it was thought this might be evidence of a shortened gestation period, but more carefully scrutinized experiments determined that this was the outcome of earlier breeding, due to an earlier maturity.

At all times this type of feeding experiment is open to the error that normally such animals exhibit very appreciable individual variations. We have anticipated that less complex life forms that show scant individual variations even in large numbers would afford acceptable data as to any action that pineal extracts might have on their growth-differentiation processes. For the purpose, we selected (1) paramoecia (paramoecium caudatum), a unicellular organism that through transverse fission may divide into many generations in a single day, (2) tadpoles of frogs and toads. This larval form of the frog and toad corresponds in many respects to embryonic intrauterine life in higher animal life.

PARAMECIUM EXPERIMENTS

Cultures were maintained in the laboratory, growing on hay infusions. These organisms are about $\frac{1}{4}$ mm. in length and may be readily counted with the naked eye. Through transverse splitting reproduction is accomplished. Under standardized conditions the rate of divisions is relatively constant. It will be argued that in the event of constant exceptional variations in the number of generations formed when pineal materials were added to the culture medium and not occurring when other similar protein materials were introduced, that the phenomenon is attributable to pineal activity. The following procedures were employed. A single paramoecium was isolated until the reproduction of the third generation. These resulting four individuals were separated and placed in different media (a) one in hay infusion; (b) one in a hay infusion extract of desiccated pineal gland, .05 per cent. strength; (c) one in a hay infusion extract of desiccated muscle of equal strength as a control material; (d) the

TABLE I. Records of Divisions of Paramoecia

| No. of Expe'm't. | 48-hour group | | | No. of Expe'm't. | 24-hour group | | |
	Hay Infusion.	Pineal Gland.	Muscle Tissue.		Hay Infusion.	Pineal Gland.	Muscle Tissue.
1	7	23	..	18	7	13	..
2	7	31	..	19	3	6	..
3	11	12	..	20	11	19	..
4	5	8	..	21	3	5	2
5	1	16	..	22	4	8	8
6	1	13		23	6	16	4
7	4	12		24	4	8	5
8	5	19	12	25	10	17	10
9	5	12	9	26	11	19	..
10	13	12	4	27	4	7	5
11	2	9	4	28	1	4	3
12	2	7	6	29	1	7	2
13	3	19	16	30	3	8	2
14	1	21	12	31	5	15	5
15	10	25	23				
16	12	30	10				
17	13	22	11				
Average	6.0	17.1	10.7		5.0	10.5	4.6

fourth one was a variable control. These cultures were maintained in a moist chamber for a fixed period (48 or 24 hours). At the expiration of that time the several cultures were examined as to the numbers of reproductions. Almost invariably the divisions were more numerous in the pineal culture. For example, in one 48-hour experiment 12 individuals resulted from the plain hay infusion, 30 individuals from the hay infusion pineal extract .05 per cent. and 10 individuals from the hay infusion muscle extract .05 per cent. The results from 31 consecutive experiments are grouped in table 1.

The inference is, that pineal materials, when added to the culture medium of the unicellular organism, paramœcium, determines a more rapid rate of reproduction. (Fig. 4).

TADPOLE EXPERIMENTS.

The time of appearance of the successtive stages in the differentiation of tadpoles into frogs is an excellent criterion of the influence of any
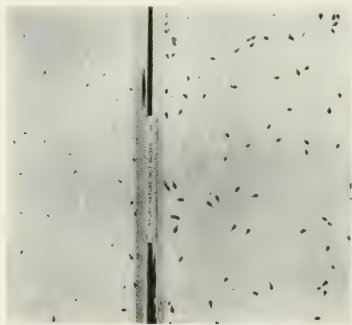
Fig. 5. A comparison of two groups of toad tadpoles taken from the same lot, photographed simultaneously after two weeks of laboratory feeding. Group to the right fed small amounts of desiccated pineal gland triweekly. Group to the left fed equivalent amounts of desiccated muscle tissue.

variation in the living conditions of these animals. For the individuals of a single laying, fairly constant is the occurrence of such stages as the budding of the hind legs with the subsequent formation of the different portions of the hind legs, the closing of the gills, the extrusion of the fore legs, the assumption of terrestrial life. Such are the phenomena we sought to influence by the introduction of pineal gland materials into the living water of the tadpoles.

About 50,000 frog eggs were procured and hatched in the laboratory. These were divided into colonies of about 200 each. In most cases these colonies were from the same laying. With so abundant materials it was possible to introduce wide variations in test materials and controls. The

pineal glands were fractionated into various components and tested against controls such as other endocrine glands, split proteins, histamine, lipoids, etc. Through photography and actual measurements the variations were recorded.

The present paper can make but most casual reference to the accumulated results. The photograph and drawings will serve to indicate the trend of results. (Fig. 5.) (Type photograph—adjacent trays of pineal fed and muscle fed tadpoles of the same laying.) At this stage the pineal fed, while about double the size of the controls, show no tendency to differ-
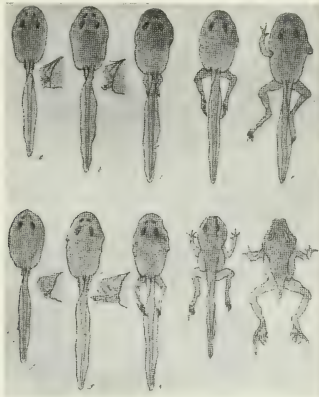
Fig. 6. Drawings made at weekly intervals indicating the rate of metamorphosis of *Bufo Americana* tadpoles fed pineal tissue in comparison with normal metamorphosis. *a* to *e* inclusive, controls. *f* to *j*, pineal fed. The small figures to the right, of *a*, *b*, *f* and *g*, represent stages in the development of the hind legs for these respective tadpoles.

entiation. Ultimately, however, differentiation is earlier, as may be observed in the drawings of Fig. 6.

It is our belief that the pineal gland contains some substance capable of stimulating growth and ultimately differentiation in these larval forms.

GENERAL SUMMARY.

From the lack of unanimity in the literature any conclusions as to the details of pineal gland function must be made flexible rather than dogmatic. A survey of available data leads to the following summary as representing the present status of the pineal as an organ of internal secretion:

1. A clinical syndrome is to be associated with disturbances of the functions of the pineal gland. Because of the involution of the pineal at puberty, the constitutional manifestations of pineal pathology appear to be confined to prepuberal years. The essential characteristics (apart from pressure and neighborhood manifestations) are (a) early sexual development evidenced in the enlarged genitalia, pubic hair, general body hair, early change in voice; (b) precocious mental development, manifested in maturity of thought and speech; (c) general overgrowth of body to the extent that a child of six or seven years may have the appearance of a child near puberty.

2. The experimental extirpation of the pineal gland is surgically possible. The gland is not essential for the maintenance of life. The early symptoms following pinealectomy are attributable to the severe brain injury. No changes attend the removal of the gland in adult animals. As to the effects of pinealectomy in young animals, Sarteschi, Foa, and Horrax respectively state that the removal of the gland leads to precocity of development. Exner and Boese, and Dandy report no changes after pinealectomy.

3. The administration of pineal substances to young mammals is reported to hasten growth and sexual maturity. In unicellular organisms (paramœcia) pineal extracts increase the rate of reproduction to more than double that of controls. In larval forms (ranidæ) both growth and differentiation are hastened as a result of pineal feeding.

4. The inference is allowable that the pineal gland is an organ of internal secretion whose functions, however, are of minor significance in the general activities of the endocrinous system.

BIBLIOGRAPHY.

EXPERIMENTAL

Anatomy and Embryology

Bezaneck, E.: Anat. Anzeiger, 1892, vii, 674. Anat. Anzeiger, 1893, viii, 669
Biondi, G.: Histologische Beobachtungen an der Zirbeldruse, Ztschr. f. d. ges. Neurol. u. Psychiat., 1912, ix, 43.
Bizzozero, G.: Centralbl. f. d. med. Wissensch., 1871, "R. Istit. Lomb. di Sc. e Lett." Milan, 1871.
Cameron, John: Anat. Anzeiger, 1903, xxiii, Proc. Roy. Soc., Edin., 1904, xxv, 162
Ramon y Cajal: Apuntes para el studio del bulbo raquideo cerebelo y origen de los nervios encefaleos, Soc. Espana Histerna Natural, Madrid, 1895.
Constantini, G.: Pathologica, 1910, ii, 439.
Cionini, A.: "Riv. Sperim. d. Fren. e. d. Med. Legale," 1885-86, xi, 182; xii, 364.
Cotugno, G.: Arch. Ital. di Anat. e di Embryol., Firenze, 1910, ix, 3-4.
Darkschewitsch, L.: Neurol. Centralbl., 1886, v, 29.
Dandy, A.: Quart Journ. of Micros. Sci., 1899, xlii, 111   Ibid 1907, li, 1   Trans Roy Soc, Lond., 1911, cci, 227-329
Dandy, A.: The Pineal Gland, Science Progress, 1907, ii, 284
Dimitriova, Z.: Recherches sur la structure de la gland pineale chez quelque mammiferes, Le Nervisne, 1901, ii, 257.
Edinger, L.: Bau der nervösen Zentralorgane, 1908, Ed. 7, 203.
d'Erchia, F.: Contributo allo studio della volta del cerebello intermedio e della regione para fisaria in embrioni di Pesci e di Mamiferi, Monitore zool. ital., 1896, vii, 118 and 201.
Faivre, E.: Observations sur le Conarium, Compt. rend. Soc. de biol., 1854, Series 2, i, 195
Faivre, E.: Ann. d. sc. nat., 1857, Series 4, Zoologie, vii-viii, 52.
Fenger, F.: The Composition and Physiologic Activity of the Pineal Gland, Journ. Am. Med Ass'n, 1916, lxvii, 1836.
Flesch, M.: Anat. Annzeiger, 1888, iii, 173.
Funkqvist, H.: Anat. Anzeiger, 1912, xlii, 111.
Galaseecu, P., and Urechia, C. J.: Les cellules acidophiles de la gland pineale, Compt. rend Soc. de biol., 1910, lxviii, 623.
Galen: De usu partium Corporis humani, Venice, 1562, viii.
Galeotti, G.: Riv. di Patol. Nerv. e. Mentale, 1896-7, ii, 481.
Gaskell, W. H.: On the origin of Vertebrates from a Crustacean-like Ancestor, Quart. Jour Micr. Sc., London, 1890, xxxi.
Hagemann: "Archiv, von Rejchert u. Du Bois-Reymond," 1872.
Hill, C.: Jour. of Morphol., 1891, v, 503.   Ibid, 1894, ix, 237.

Hoskins, E. R.: The growth of the body of the Albino rat as affected by feeding various ductless glands (thyroid, thymus, hypophysis and pineal), Jour. of Exp. Zoology, 1916, xxi, 295.

Illing, P.: Vergl. anat. u. histol. Unters. u. d. Epiphysis, etc. Inaug Dissert. Leipzig, 1910.

Jordan, H. E.: Histogenesis of Pineal Body of Sheep, Am. Jour. Anat. 1911-12, xll, 249.

Jordan, H. E.: Results of Recent Studies of the Mammalian Epiphysis Cerebri, Tr. Am. Micr. Soc., 1911, xxx. 231.

Jordan, H. E.: Anatomical Record, 1911, v, 325.

Kölliker, A.: Microscopische Anatomie des Menschen, Leipzig, 1850, ii

Krabbe, K.: Sur la gland pineale chez l'homme (Nouv. iconog. de la Saltpetriere, 1911, Hist Univers, or Corp. Pin. Copenhagen, J. Gjellerup, 1915.

Legos: "These de Paris." (A pathological study), 1873.

Leydig, F.: "Traite d'Histol. Compt. de l'Homme et des Animeux," 1868, 399

Locy, W. A.: Anat. Anzeiger, 1893, ix, 169, 231, 486. Jour. of Morphol., 1893, ix, 115, 1894; xi, 497.

Luys: Systeme Nerveux Cerebro-spinal. 1865.

Meynert, T.: Stricker's Handbuch, 1871, Chap. 31.

Munzer, A.: Die Zirbeldruse, Berlin, klin. Wochschr., 1911, xlviii, 1669.

Nicolas, A.: Compt. Rend. d. l. Soc. de Biol., 1900, lii, 876.

Obersteiner: Anleitung beim Studium des nervosen Zentralorgane, 1901, iv.

Peytoureau, S. A.: "These de Bordeaux," 1886-87, 68.

Poppi: "L'Iponisi cerebrale, faringea e la glandula pineale in Patologia," etc., etc., 1911

Reichert, C. B.: Der Bau des menschlichen Gehirns, Leipzig, 1859, Part 2, 69.

Retzius, G.: Das Menschenhirn, Stockholm, 1896, 54.

Sarteschi, U.: Richerche istologiche sulla ghiandola pineale, Folia neurobiol, 1910, iv, 675.

Schwalbe, G.: Lehrbuch der Neurologic, Erlangen, 1881.

Seignent, P.: "These de Paris," 1912, 119.

Sorenson, A. D.: Journ. of Comparative Neurol., 1894, iv, 153.

Stadelini, R.: Monit. Zool. Ital., 1897, viii, 241.

Streeter: Mall-Kaibel, 1912, ii, 81.

Studnicka, F. S.: Die Parietalorcane, Oppel's Lehrbuch der vergl. mikroskopische Anatomie der Wirbeltiere, 1905, Part 5, Jena (Monograph).

Sauvy: "Systeme Nerveux Central," 1889, ii, 781

Walter: Beitrag zur Histologie der menschen, Zirbeldruse, Zeitschr. f. d. ges. Neurol. u Psychiat., Berlin and Leipzig, 1913, xvii, 65.

Warren, J.: The Development of the Paraphysis and Pineal Region in Reptilia, Am. Jour. Anat., 1911, ii, 313.

Weigert, C.: "Beitrage z. Kenntniss d. normalen mensch Neuroglia." 1895.

v. Mihalkovicz, V.: "Entwick-Geschichte des Gehirns," 1877, 98.

Voeltzkow, A.: "Abh. d. Senckenberg, naturf. Gesellsch," 1903, xxvii.

Bisch, P. and Hulles, E.: Ueber die Beziehungen der Zirbeldruse sur Genitale, Wien. klin. Wehnschr., 1912, xxv.

Von Cyon, E.: Zur Physiologie der Zirbeldrüse, Arch. f. d. ges. Physiol., 1903, xcviii, 327.

Dixon, W. E., and Halliburton, W. D.: The Pineal Body, Quart. Jour. Exper. Physiol., 1909, ii, 283.

Dixon and Halliburton: Proc. Physiol. Soc. (Journ. of Physiol.), 1910, xl, 30.

Howell, W. H.: The Physiological Effects of Extracts of the Hypophysis Cerebri and Infundibule Body, Jour. Exper. Med., 1898, iii, 245.

Jordan, H. E., and Eyster, J. A. E.: The Physiological Action of Extracts of the Pineal Body, Am. Jour. Physiol., 1911, xxix, 115.

Loewy, P.: Die Secretwege der Zirbeldrüse, Arb. a. d. neurol. Inst. a. d. Wien. Univ., 1912, xx, 130

Mackenzie, K.: Quart. Journ. of Exper. Physiol., 1911, iv, 317

Novak, J.: Ueber Künstliche Tumoren der Zirbeldrüsengegend, Wien. klin. Wchnschr., 1914, xxvii,

Ott, J. and Scott, J. C.: The Action of Corpus Luteum and of the Pineal Body, Month. Cycl. and Med. Bull., 1912, 207.

Ott, J., and Scott, J. C.: Proc. Soc. Exper. Biol. and Med., 1910. Therapeutic Gazette, 1911, xxvii, 68. Therapeutic Gazette, 1912, xxviii, 310.

Pellegrine: Gli. effette della castrazione sulla ghiandola pineale, Arch. p. le sc. med., 1914, xxxviii, 121.

Sainton and Dagnan-Bouveret: Descartes et psychophysiologie de la glande pineale, Nouv. iconog. de la Saltpetriere, 1913, xxv, 71-192.

Extirpations

Adler: Extirpation der Epiphy-e, Arch. f. Entwicklung-mechn d. Organ, 1914, xl, 1

Exner, A., and Boese, J.: Ueber experim. Extirpation der glandula pineale, Munchen med Wchnschr., 1911, 154; Neurol. Centralbl., 1910, 754.

Exner, A., and Boese, J.: Deutsch. Zeit-ch. f chrurg., 1910, cvii, 182.

Foa, C.: Hypertrophie des testicules et de la crete apres l'extirpation de la gland pineale chez le coq, Arch. ital. de biol., 1912, lvii, 233.

Foa, C.: Nouvelles recherches sur la fonction de la gland pineale, Arch. ital. de biol., 1914, lxi, 79.

Sarteschi, U.: Richerche istologiche sulla ghiandola pineale, Folia neurobiol., 1910, iv, 675.

Sarteschi, U.: Sindrome epifisaria macrogenitosmia praecox, Pathologica, 1913, v, 707.

Dandy, W. E.: Extirpation of the Pineal Body, Jour. Exper. Med., 1915, xxii, 2.

Horrax, G.: Vide infra.

Feeding Experiments

Berkeley, W. N.: The Use of Pineal Gland in the Treatment of Certain Classes of Defective Children, Med. Rec., New York, 1914, lxxxv, 513.

Dana, C. L., and Berkeley, W. N.: The Functions of the Pineal Gland, Med. Rec., New York, 1913, lxxxiii, 835.

Goestch, E.: The Influence of Pituitary Feeding upon Growth and Sexual Development, Bull. Johns Hopkins Hosp., 1916, xxvii, 29.

Gudernatsch: Feeding Experiments on Tadpoles, Am. Jour. Anat., 1914, xv, 431.

Hofstatter, R.: Diskussion zu v. Frankl-Hochwart, Verein f. Psychiat. u. Neurol. in Wien, 1913.

Horrax, G.: Studies on the Pineal Gland, I, Experimental Observations, Archives of Internal Medicine, 1916, xvii, 607-626.

McCord, C. P.: The Pineal Gland in Relation to Somatic, Sexual and Mental Development, Jour. Am. Med. Assn., 1914, lxiii, 232.

McCord, C. P.: The Pineal Gland in Relation to Somatic, Sexual and Mental Development, No. II, Journ. Am. Med. Assn., 1915, lxv, 517.
McCord, C. P.: The Pineal Gland, Interstate Med. Jour., 1915, xxii, 354.

General

Benda: Deutsch. Klin., 1903.
Biedl: Innere Secretion, Urban and Schwarzenberg, Vienna, 1913.
Cushing, H.: The Pituitary Body and Its Disorders, J. B. Lippincott Co., 1912.
Erdheim: Wien Akad. Sitzkb., 1904, cxiii.
Fröhch: Wien. klin. Rundschau, 1904, xlvii, 48.
Fischer, B.: Hypophysis, Akromegalie und Fettsucht, Wiesbaden, Bergman, 1910.
Kidd, L. J.: The Pineal Body. A Review, Rev. Neurol. and Psychiat., 1913, 1.
Munzer, A.: Die Zirbeldrüse, Berl. klin. Wchnschr., 1911, xxxvii, 1.
Vincent, S.: Internal Secretion and the Ductless Glands, 1912.
Schuller, A.: Lewandowsky's Handbuch der Neurologie, 1913, iv, 337.
Marburg, O.: Zur Kenntniss der normalen and pathologischen Histologie der Zirbeldrüse, Arb. a. d. neurol. Inst. Obersteiner, Wien, 1909, xvii, 217.
Del Priere, N.: Modifications dans la pression Sanguine et dans l'accroissement somatique des lapine, a suite d'injections d'extrait de glande pineale, Arch. Ital. de Biol., 1915, lxiii, 122.

Clinical

Askanazy, M.: Teratom und Chorionepitheliom der Zirbeldrüse, Verhandl. d. deutsch. path. Gesellsch., Jena, 1906, 58.
Bailey and Jelliffe: Tumors of the Pineal Body, The Archives Int. Med., 1911, viii, 851.
Bartlett, F. K.: Hypertrophy of Pineal Gland, The Archives Int. Med., 1913, xii, 201.
Biach and Hulles: Ueber die Beziehungen der Zirbeldrüse zum Genitale, Wien. klin. Wchnschr., 1912.
Blane, G.: History of Some Cases of Disease in the Brain; Case of a Tumor Found in the Situation of the Pineal Gland, Tr. Soc. Imp. Med. and Surg. Knowledge, 1800, ii, 198.
Blanquinque: Tumeur de la glande pineale, Gaz. hebd., 1871, 532; Lancet, London, 1871.
Bouchut, M.: Kyste du troisième ventricule avec hydrocephalie des ventricules lateraux, Gaz. d. hop., 1872, xliii, 353.
Campbell, A. W.: Notes of Two Cases of Dilatation of the Central Cavity or Ventricle of the Pineal Gland, Tr. Path. Soc., London, 1894, i, 15.
Chirone, P.: I tumori della glandula pineale, Med., ital., 1907, v, 141.
Coats, J.: An Adenoid Sarcoma with Cartilage Originating in the Pineal Gland, Tr. Path. Soc., London, 1887, xxxviii, 44.
Cushing, H.: The Pituitary Body and Its Disorders, J. B. Lippincott Co., 1912.
Daly: A Case of Tumor of the Pineal Gland, Brain, 1888, x, 234.
Duffin: Tumor Implicating the Corpora Quadrigemina, Clin. Soc., London Lancet, London, 1876, i, 888.
Eberth, J.: Intrakranielles Teratom mesodermalen Ursprungs, Virchow's Arch. f. path. Anat., 1898, cliii, 71.
Esteves and Beatti: Klinische und anatomische Studien eines Epithelioms der Zirbeldrüse, Arch. de Pedagogia de la Plata, 1909.
Falkson, R.: Ein Chondrocystosarkom im dritten Ventrikel, Virchow's Arch. f. path. Anat., 1879, lxxv, 550.
Feilschenfeld: Ein Fall von Tumor cerebri (Gliasarkom) der Zirbeldrüse Neurol. Centralbl., 1885, iv, 409.
Förster: Ein Fall von Markschwamm mit ungewöhnlich vielfacher metastaticher Verbreitung, Virchow's Arch. f. path. Anat., 1858, xiii, 271.
Frankl-Hochwart: Ueber Diagnose der Zirbeldrüsentumoren, Deutsch Ztschr. f. Nervenh., 1909, xxxvii, 455.
Frankl-Hochwart: Wien. med. Wochschr., 1910, ix, 505.
Freidreich: Psammoma kystomatosum hämorrhagicum der Glandula pinealis in Kombination mit Medullarsarkom, Virchow's Arch. f. path. Anat., 1863, xxxiii, 165.
Frou: Inflammation méninges avec reactions chromatique, hbrinese et leucocytique du liquide cephalo-rachidien, Gaz. d. hop., 1963
Garrod, A. E.: Pineal Cyst, Tr. Path. Soc., London, 1899, i, 14.
Gaudery, J.: Zur Kasuistik der Zirbeldrüsentumoren (Teratoma glandulæ pinealis), Inaug. Dissert, Giessen, 1899.
Goldzeiher, U.: Ueber eine Zirbeldrüsengeschwulst, Virchow's Arch. f. path. Anat., 1913, ccxii, 353.
Gowers: Cases of Cerebral Tumors, Lancet, London, 1879, 394.
Gutzeit, R.: Ein Teratom der Zirbeldrüse, Inaug. Dissert, Königsberg, 1896.
Hart, C.: Ein Fall von Angiosarkom der Glandula pinealis, Berl. klin. Wchnschr., 1909, xlvi, 2298.
Hedenius, I., and Henschen, F.: Tumor in Pineal Gland, Hygeia, Stockholm, 1913, lxxv, 226.
Hempel, M.: Ein Beitrag zur Pathologie der Glandula pinealis, Inaug. Dissert, Leipzig, 1901.
Heubner: Demonstration before the Versammlung deutscher Naturforscher und Aerzte, Düseldorf, 1898, Allg. med. Centr. Ztg., 1899, lxviii, 89.
Hijmans van der Bergh and van Hasselt: Tumor glandulæ pinealis, sive epiphysis cerebri, Nederl. Tijdschr. v. Geneesk., 1913, i, 1271.
Horrax: Studies on the pineal gland II Clinical Observation, Archives of Internal Medicine, 1916, xvii, 627 645.
Hösslin, R. V.: Tumor der Epiphysis cerebri, München. med. Wchnschr., 1894.
Howell: Tumors of the Pineal Body, Proc. Roy. Soc. Med., 1910, iii, 65.
Hueter: Teratorum der Zirbeldrüse, München, Med. Wchnschr., 1913, 895.
Jonkovsky, V.: Hydrocephalie et tumeur congenitale de la glande pineale chez un nouveau ne, Rev. mens. d. mal. de l'enf., 1901, xix, 197.
Kny, E.: Fall von isoliertem Tumor der Zirbeldrüse, Neurol. Centralbl., 1889, viii, 281.
König, E.: Ueber ein Psammosarkom der Zirbeldrüse, Inaug. Dissert, München, 1894.
Lawrence, T. W. P.: Tumor of Pineal Body, Tr. Path. Soc., London, 1899, l.
Lord, J. R.: The Pineal Gland; its Normal Structure; Some General Remarks on its Pathology; a Case of Syphilitic Enlargement, Tr. Path. Soc., London, 1899, 1.
Marburg, O.: Zur Kenntniss der normalen und pathologischen Histologie der Zirbeldrüse, Arb. a. d. neurol. Inst. Obersteiner, Wien, 1909, xvii, 217; Die Adipositas Cerebralis, Wien. Med. Wchnschr., 1908, lviii, 2617; ibid, 1907, lii.

Marburg, O.: Die Klinik der Zerbeldrüse Krankungen, Ergebn. d. inn. Med. u. Kinderh., 1913, x, 146.

Machell, H. T.: The Canadian Lancet, 1911, 171. "Report of two cases of sexual precocity"

Massot: Note sur un cas de tumeur cerebrale avec polyurie, Lyon med., 1872, x.

Mestrezat, W.: Le liquide cephalo-rachidien, normal et pathologique, Paris, 1912.

Meyer, A.: Adenoma of the Pineal Gland, Jour. Nerv. and Ment. Dis., 1903, xxx, 216; ibid., 1905, xxxii, 464.

Morse, J. L.: A Case of Abnormal Physical and Sexual Development in an Infant of Two Years; Probably due to a Tumor of the Pineal Gland, Arch. Pediat., March, 1913. 1.

Mueller, E.: Ueber die Beeinflussung der Menstruation durch cerebrale Heiderkrankungen, Neurol. Centralbl., 1905, 790.

Münzer, A.: Pubertas praecox und psychische Entwickelung, Berl. klin. Wchn-chr., 1914, x, 1.

Nassetti, F.: Contributo allo conocenza dei tumori della gl. pineali, Atti. d. r. Acad. d fisiocrit di Siena, 1912, v, 19.

Nassetti, F.: Pineal cysts, Riv. sper. di freniat, Reggio-Emilia, 1912, xxxviii, 291

Neumann, M.: Zur Kenntniss der Zirbeldrüsengeschwulste, Monatschr. f. Psychiat. u. Neurol., 1901, ix, 337.

Neumann, P.: Ein neuer Fall von Teratom der Zirbeldrü-e, Inaug. Dissert. Königsberg, 1900

Niccolai, N.: Contributo clinico adlo studio delle sindromi epifisarie e funzione endocrine, Riv. crit. di clin. med. Firenze, 1914, ٢v, 241 and 257.

Nieden: Fall von Tumor (hydrops cysticus) glandulæ pinealis, Centralbl. f. Nervenh. 1879, ii, 169.

Nothnagel: Topische Diagnostik der Gehirnkrankheiten, Berlin, 1879, 206.

Nothnagel: Geschwulst der Vierhugel, Wiener med. Bl., 1888, 162, 193, 225.

Oestreich and Slawyk: Riesenwuchs und Zirbeldrusengeschwulst, Virchow's Arch. f. path Anat., 1899, clvii, 475.

Ogle, C.: Sarcoma of Pineal Body, Tr. Path. Soc., London, 1899 (two cases).

Pappenheimer: Ueber Geschwülste des Corpus pineale, Virchow's Arch. f. path. Anat., 1910, cc.

Pellizzi, G. B.: Riv. Ital. d. Neuropatol, etc., 1910, iii, 193; Lavorii d. Ist. d. Clin. d. Mal. Nerv. d. R. Univ. d. Pisa, 1910, ii.

Pineales: Beziehungen der Akromegalie zum Myxödem, Samml. klin. Vortr., New Series, 1899, 242.

Pontoppidan, K.: Ein Fall von Tumor der Zirbeldrüse, Neurol. Centralbl., 1885, 553.

Raymond and Claude: Les tumeurs de la gland pineale chez l'enfant, Bull. de l'Acad. de med., 1910.

Reinhold, H.: Ein Fall von Tumor der Zirbeddrüse, Inaug. Dissert, Leipzig, 1886.

Rorschach, H.: Zur Pathologie und Operabilität der Tumoren der Zirbeldrüse, Beitr. z. klin. Chir., 1913, lxxxviii, 451.

Russel, J. E.: Cysts of the Pineal Body, Tr. Path. Soc., London, 1899, i, 15.

Schearer: Enlargement of the Pineal Gland and Sclerosis of Brain in a Case of Chronic Epilepsy with Amentia and Aphasia, Edinburgh Med. Jour., 1875, xxi, 297.

Schmid, C.: Ueber latente Hirnherde, Virchow's Arch. f. path. Anat., 1893, cxxxiv, 93.

Schmidt, P.: Beiträge Zur Diagnostik der Krankheiten des Gehirns, Med. Diag., 1837, vi, 32.

Schultz, R.: Tumor der Zirbeldrüse, Neurol. Centralbl., 1886, 439.

Segarey, A.: Les tumeurs de la glande pineale, Gaz. d. hop., Paris, 1914, lxxxvii, 1141-1205.

Simon, E.: Hemorrhagia de la gland pineale, Bull. Soc. Anat., Paris, 1859, xxxiv, 306.

Stanley, S.: Dropsy of the Pineal Gland, Lancet, London, 1837, 935.

Thomas: Ueber riesenwuchsähnliche Zustände in Kindesalte, Ztschr. f. Kinderh., 1912, v, 401-430.

Timme, W., and Bailey, P.: A Contribution to the Pathogenesis of Progressive Muscular Dysatrophy, with the Consideration of Evidence Connecting this Disease with Disturbances in Endocrine Glands. (Abstract) Program 67th Annual Session Am. Med. Assn., 1916, 114.

Turner, F. Ch.: Spindle Cell Sarcoma of Pineal Body, Containing Glandular and Carcinomatous Structures, Tr. Path. Soc., London, 1885, xxxvi, 27.

Van der Heide, C. C.: Tumor glandular pinealis sive epiphysis cerebri, Nederl. maandscher. v. verlosk. en vronwenz en v. kindernessk., Leiden, 1914, iii, 253-260.

Verger, M.: Gliosarcoma develope au niveau de la glande pineale, Jour. de med. de Bordeaux, 1907, xxxvii, 216.

Verger, M.: Teratom und Chorioephitheliom der Zirbeldrüse, Verhandl. d. deutsch. path. Gesellsch., 1906, 58.

Vikhodtseff, S. N.: Disease of Pineal Body with Involvement of the Eyes and Acromegaly, Vestnik Ophthalmol., Moskow, 1913, xx, 1014.

Virchow, R.: Krankhafte Geschwülste, Berlin, 1863, i.

Weed, L. H, and Cushing, H.: Studies on Cerebrospinal Fluid. viii, Amer. Jour. of Physiology, 1915, xxxvi.

Weigert, C.: Zur Lehre von den Tumoren der Hirnanhänge, Virchow's Arch. f. path. Anat., 1875, lxv, 212.

Wernicke: Lehrbuch der Gehirnkrankheiten, 1883, iii, 299.

Weisenburg, T. H.: Brain, 1910, xxxiii, 236.

Wolff: Zirbeldrüsenextrakt in der geburtshilflichen Landpraxis, Deutsch. med. Wchnschr., 1913, xxxix, 1557.

Zenner, A.: A Case of Tumor of the Pineal Gland, Alienist and Neurol., 1892, xiii, 470.

Ziegler: Lehrburch der patholovischen Anatomie, Ed. 4, 620.

THE NUCLEAUS CARDIACUS NERVI VAGI AND THE THREE DISTINCT TYPES OF NERVE CELLS WHICH INNERVATE THE THREE DIFFERENT TYPES OF MUSCLE..*

Edward F. Malone

Cincinnati.

THREE FIGURES.

When one has carefully and critically studied in series of Nissl preparations the brains of various mammals, there is revealed the presence of constant cell groups whose cells invariably possess certain definite characteristics as to size, form and structure. A separation of two groups of cells based merely upon differences in their histological characters is justified in the present state of our knowledge, only when such differences are constant and striking. When these conditions are fulfilled we may conclude that such constant and striking differences in cell character correspond to a difference in cell activity, just as in other portions of the body. I have pointed out elsewhere that very real differences in cell character have been neglected by experimental workers, and that their results have been rendered thereby of less value. Since the dorsal motor (sympathetic) nucleus of the vagus is known to contain centers for the control of both heart muscle and smooth muscle, one would suppose that any real difference in the cell character of various portions of this nucleus would at once claim the attention of the experimental worker and that he would attempt to inform us as to the relation of these different types of cells to the various functions of the vagus nerve. But such is not the case; we are informed casually that some cells are large and others small, and thereafter the cells are considered as if they were all of the same type.

The discovery of two different types of cells in the sympathetic vagus nucleus was not accidental; I was led to look for this difference on the following grounds. In the first place, I had recently shown that all cells concerned in transmitting efferent impulses to striated muscle possess a fundamental similarity of structure, whether the axone of the cell be in direct relation to the muscle or whether the cell act on the muscle through the mediation of one or more efferent neurones. This observation naturally strengthened my belief in the significance of the relation of cell character to cell function. In the second place, I had observed the striking difference between the cells supplying striated and those supplying smooth muscle. Since in a recent paper Molhant had shown that all fibers of the vagus supplying heart and smooth muscle arise from the sympathetic vagus nucleus, I concluded that in cells having such diverse functions there must exist a fundamental difference in histological character. As was anticipated, two different types of cells were found; the evidence in favor of ascribing to the cells of one type the innervation of heart muscle, and on the other

hand, to cells of the other type the innervation of smooth muscle, will be considered later.

The material available consisted of two complete series. The first was a series of the brain of a lemur, while the second was of the brain of macacus rhesus. Both brains were fixed in 95 per cent. alcohol, and after the usual treatment with absolute and chloroform, were imbedded in paraffin. Serial sections were stained in a 1 per cent. aqueous solution of toluidin blue (Grübler), differentiated in 95 per cent. alcohol, dehydrated in absolute, cleared in xylol, and mounted in Canada balsam. Series of brains of other forms will have to be prepared and studied before I feel justified in committing myself upon many points, and the present article has therefore been limited, especially as to the exact location and distribution of the different types of cells.

The efferent fibers of the vagus nerve arise from two distinct columns of cells. From the nucleus ambiguus arise the fibers which supply striated muscle, while from the so-called dorsal motor nucleus arise fibers which innervate heart muscle and smooth muscle. This fundamental difference as to function, which has been proved beyond doubt by the recent investigation of Molhant, had not been clearly recognized; this obscurity was probably favored by the fact that the nucleus ambiguus, together with the motor nuclei of the eleventh, seventh and fifth cranial nerves have often been regraded as visceral, regardless of the fact that their cells cannot be distinguished either histologically or functionally from the cells of the other motor nerves supplying striated muscle. Thus this classification giving undue emphasis to a condition which in mammals no longer exists, has contributed to the general lack of appreciation that the dorsal motor nucleus of the vagus is composed of cells which differ radically both histologically and functionally from those of the nuclei supplying striated muscle, regardless of whether the striated muscle be of somatic or of visceral origin. The name "dorsal motor nucleus" does not indicate the true function of this cell group, and I shall use the name "sympathetic or visceral nucleus of the vagus."

The location and extent of the sympathetic nucleus of the vagus is well known and will not be considered in this paper, except to call attention to the fact that it extends as a long column of cells dorso-lateral to the hypo-. glossus nucleus from the lowest portion of the medulla to almost the level of the oral pole of the inferior olive. An excellent description of the location of this nucleus is given in Jacobsohn's monograph. The oral portion of the nucleus is composed of small cells of the type shown in figure 2; this is true both in the case of the lemur and the monkey. As one follows the nucleus caudally a second type of cell begins to appear (Fig. 1). The portion of the nucleus in which both types of cells occur is at the level of the oral portion of the hypoglossus nucleus, and here the sympathetic nucleus attains its greatest diameter. The cells of each type are partly separated from each other, although no sharp line of separation is evident. In the

lemur the large cells (Fig. 1) form a fairly compact group dorsal from the small cells, whereas in the monkey their relative position is reversed. Proceeding further in a caudal direction, the small cells become rapidly less numerous and finally disappear. After the disappearance of the small cells the sympathetic nucleus, consisting now entirely of the large cells (Fig. 1) proceeds caudally as a well developed and definite group. In the most caudal portion of the medulla the sympathetic nucleus is much reduced; only a few cells are seen in each section, and these cells become smaller and have the appearance of the smallest cell in figure 1; in this portion of the nucleus (the caudal end) are probably also cells of the type shown in figure 2, that is, similar to those in the oral portion of the nucleus, but at present I cannot be absolutely sure of this, as the surrounding cell groups have not been sufficiently studied. The smallest cell shown in figure 1 is probably a transition type between the other cells of figure 1, and those of figure 2. To sum up, the sympathetic vagus nucleus consists of three portions: (a) an oral portion whose cells are of the type in figure 2; (b) a middle portion whose cells are shown in figure 1; and (c) a caudal portion composed of cells shown in figure 2 (same as oral portion) and also of cells such as the smallest cell in figure 1 (probably a transition type).

It is not my intention to present in this paper a detailed description of the types of cells in the vagus sympathetic nucleus, but rather to point out the fact that there are very definite differences in histological character between the cells of the various groups; a study of the illustrations will make this evident. Since these differences in cell character exist, and since such differences must necessarily be an indication of corresponding differences of cell activity, we may now consider whether these different cell groups of different character may be brought into relation with definite functions. In the first place, it has been shown by Molhant, in his excellent and extensive work on the vagus nerve, that the sympathetic nucleus of the vagus gives origin to all the fibers of the vagus which supply smooth and heart muscle, and that all its cells give origin to such fibers. Further, he has shown that the oral portion supplies smooth muscle (stomach, lungs), the function of the extreme caudal portion is doubtful (possibly connected with the trachea and bronchi), while the intermediate portion supplies heart muscle, but he has failed to connect these different functions with different types of cells. Concerning the function of the caudal portion of the nucleus, which is composed of cells of the type shown in figure 2, together with cells resembling the smallest cell of figure 1, we can draw no definite conclusion. The oral portion consists exclusively of the type of cells shown in figure 2, and we may conclude that this type of cell supplies smooth muscle; of course this does not justify us in concluding that this type of cell (Fig. 2) is the only type of cell which may supply smooth muscle, or that this type may not in other regions have a different function. Overlapping the cells supplying smooth muscle (Fig. 2) and extending caudally unaccompanied by other types of cells is the type of cell shown in figure 1, and this portion

of the sympathetic nucleus has been shown (Molhant) to supply heart muscle.

It is evident therefore that the cells of figure 1 supply heart muscle, while those of figure 2 supply smooth muscle (stomach and lungs). In addition there is purely histological evidence to support the functional relations of these two types of cells (Figs. 1 and 2), *since the cells supplying heart muscle* (Fig. 1) *are a type intermediate in histological structure between those supplying smooth muscle* (Fig. 2) *and those supplying striated muscle* (cells of hypoglossus nucleus, Fig. 3). The relative size of the Nissl bodies in the three types of motor cells illustrated in figures 1 to 3 is especially worthy of notice. The fact that nerve cells supplying heart muscle are of a type intermediate between those supplying striated and smooth muscle constitutes one of the strongest arguments in support of the importance of the relation of cell character to cell function, since heart muscle is histologically intermediate between the two other types of muscle.

The cell group which supplies heart muscle, composed of the characteristic cells shown in figure 1, I shall name provisionally "nucleus cardiacus nervi vagi." I do not feel justified in assigning any name to the other portions of the vagus sympathetic nucleus, but shall be content with pointing out that the cells of the oral portion which supply smooth muscle are of a definite type (Fig. 2). A further division is at present not advisable because the functional relations of the caudal group are not understood, and because the pigmented cells described by Jacobsohn in man, have not been identified and studied (of course, in lower animals pigment is wanting, although homologous non-pigmented cells may exist). Further subdivision of the sympathetic nucleus, together with a detailed description of the location and extent of the various cell types, the consideration of transition types, and of the relations of the nucleus to the cells of surrounding nuclei, must await a thorough study of numerous series of various animals (including man).

CONCLUSIONS.

1. The histological character of a nerve cell is an indication of its function. Differences in connections with portions of the organism which differ merely in spatial relations do not involve a difference in the character of the nerve cells, but are associated merely with the *location* of the nerve cell; for instance, arm and leg muscles, flexors and extensors are all innervated by the same type of cell, although such differences in peripheral connections correspond to differences in the position of the corresponding nerve cells.

2. The three types of muscle are innervated by three distinct type of nerve cell, which, however, are related to one another in such a manner that the cell innervating heart muscle is of a type intermediate between the other two types of cells. Heart muscle, smooth muscle, and striated muscle are innervated by cells such as are illustrated in figures 1, 2 and 3 respec-

PLATE I

NUCLEUS CARDIACUS NERVI VAGI

Edward F. Malone
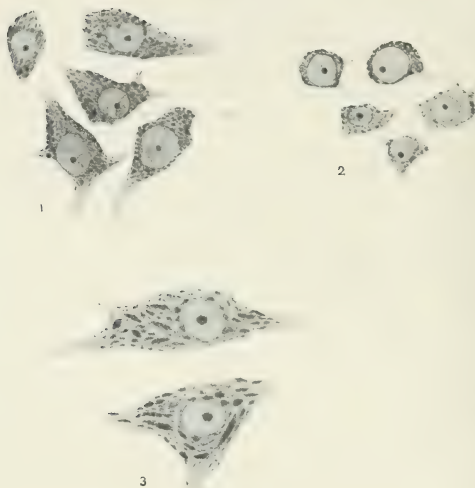
PLATE I.

Explanation of Figures.

1 to 3. The cells illustrated in the three figures were all drawn from the same section with the aid of the camera lucida, and for all cells the magnification is 580 diameters. I have attempted to reproduce as nearly as possible the actual appearance of the cells, combining to a certain extent different levels of focus. These three figures clearly show that the cells supplying heart muscle (Fig. 1) are histologically intermediate between the cells supplying smooth muscle (Fig. 2) and those supplying striated muscle (Fig. 3).

1. Cells from nucleus cardiacus nervi vagi of lemur. The smallest cell represents probably a transition type to the cell type of figure 2, and this type occurs more frequently in the caudal portion of the vagus sympathetic nucleus where it is found together with the cells of the type shown in figure 2. 580 diameters.

2. Cells of vagus sympathetic nucleus of lemur which innervate smooth muscle. In the oral portion of the sympathetic vagus nucleus these cells occur alone; more caudally they occur together with the cells of the nucleus cardiacus (Fig. 1) in the most oral portion of this nucleus. In the caudal portion of the sympathetic nucleus such cells probably reappear and are accompanied by the small cell type shown in figure 1 (smallest cell). 580 diameters.

3. Cells from hypoglossus nucleus of lemur, innervating striated muscle. 580 diameters.

tively, the cells of figure 1 constituting a type intermediate between the other two.

3. The nucleus cardiacus nervi vagi is situated in the middle portion of the sympathetic nucleus of the vagus and is composed of cells shown in figure 1.

4. The time has passed when experimental workers can afford to neglect to inform themselves of the existence of definite types of cells situated in the region under investigation, and to attempt to bring cell character into relation with cell function.

BIBLIOGRAPHY.

Jacobson, L., 1909: Über die Kerne des menschlichen Hirnstamms. Aus dem Anhang zu den Abhandlungen der königl. preuss. Akad. d. Wiss.

Malone, E., 1910: Über die Kerne des menschlichen Diencephalon. Aus dem Anhang zu den Abhandlungen der königl. preuss. Akad. d. Wiss.

Malone, E., 1913: Recognition of members of the somatic motor chain of nerve cells, etc. Anat. Rec., vol. 7, No. 3.

Molhant, M., 1910: Le nerf vague (primière partie). Le Névraxe, tom. 11.

Molhant, M., et Van Gehuchten, A., 1912: Contribution a l'étude anatomique du nerf pneumogastrique chez l'homme. Le névraxe, tom. 13.

A PHARMACOLOGICAL STUDY OF BENZYL BENZOATE.*

By Edward C. Mason, A. B., M. D., and Carl E. Pieck, B. S.,

Cincinnati.

The recent introduction of benzyl benzoate to the medical profession, and the apparently increasing demand for the substance have led us to undertake the present study in the hope of adding some further contribution to our knowledge of the pharmacologic action of the body. With reference to this type of benzyl derivatives it has already been stated by Macht that "inasmuch as they are practically insoluble in water, pharmacologic experiments with them could not be performed on isolated tissue *in vitro* except under special conditions." We have, of course, been confronted with this difficulty in carrying out the present experiments which have been performed entirely on the intact animal, since Macht,[1] in his splendid work on this subject, has probably done all that would yield valuable information through working with isolated tissues.

Three different preparations were used in the course of this work. They were sold by the following firms: Hynson, Westcott and Dunning, Baltimore; The Norwich Pharmacal Co., Norwich, N. Y., and Van Dyke and Co., New York. These three preparations varied somewhat in toxicity, and considerably in their property of remaining in solution. However, the pharmacologic effects produced were quite the same. By testing the action on drawn blood we found that these commercial 20 per cent. preparations exercised a pronounced action on the drawn blood, and for that reason we have used the 20 per cent. preparations diluted with an equal volume of water. We found this 10 per cent. dilution very satisfactory for intravenous injection. In many of our records the term "saturated water emulsion" is used and is not technically correct, but refers to the 10 per cent. solution just described.

In the recent medical literature[2] a considerable number and variety of clinical conditions are described as having been benefited, often in a very striking manner, by the use of the benzyl esters. Among these conditions may be mentioned (1) excessive peristalsis of the intestine, as in diarrhea and dysentery, (2) intestinal colic and enterospasm, (3) pylorospasm, (4) spastic constipation in which there was a tonic spastic condition of the intestine, (5) biliary colic, (6) ureteral or renal colic, (7) vesical spasm of the urinary bladder, (8) spasmodic pains originating from the contraction of the seminal vesicles, (9) uterine colic, (10) arterial spasm, including hypertension or high blood pressure, (11) bronchial spasm. It has been our aim in this study to shed some light, if possible, on the mechanism by which these conditions are relieved, and to ascertain the concentration of the drug in the blood necessary to produce the desired results.

It will be noted that the first four clinical conditions listed above refer to increased activity or increased tonus of the intestinal tract. We have
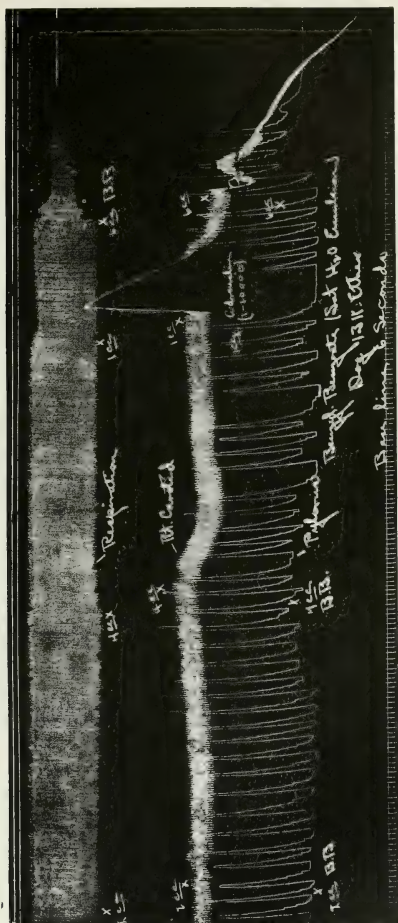
Figure 1.

therefore felt it desirable to study the nature of the relaxation produced by the benzyl benzoate in these conditions. Figure 1 shows the respiration, right carotid pressure and pylorus contractions in a dog weighing 13 kilos. Near the beginning (left) of the tracing 2 cc. benzyl benzoate solution was injected into the femoral vein. This produced no appreciable change in the rate or amplitude of either the pyloric contractions or the respiration. There is perhaps a slight change in the blood pressure tracing. Following this
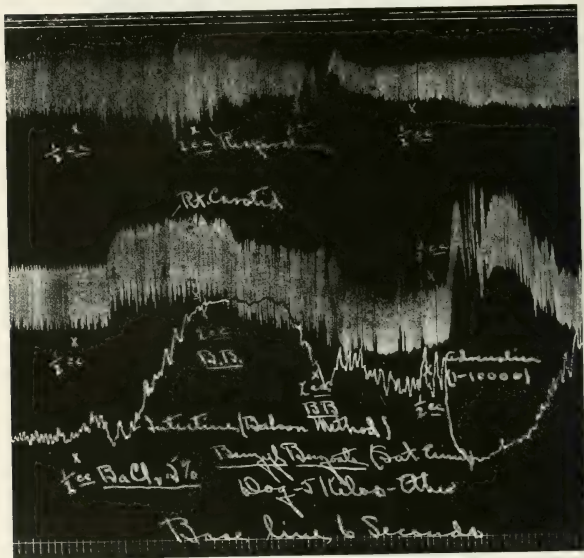
Figure 2.

4 cc. of the benzyl benzoate solution was injected and this produced a depression of the respiration, an obvious fall in blood pressure and perhaps a very slight inhibitory effect on the pyloric contractions. An injection of 1 cc. of adrenaline (1-10,000) was now given as a check on the technic of the experiment. This produced a very obvious, but rather brief, inhibition of the pyloric contractions. When the animal again returned to normal a further injection of 6 cc. of benzyl benzoate was given. After a brief interval this

dosage produced complete relaxation of the pylorus, but simultaneously it caused the death of the animal, apparently by central respiratory paralysis. This tracing shows very well the progressive effects of small, medium and large doses of the drug. The marked slowing of the heart following the 4 cc. injection should be noted.

In order to get further information regarding the action of the drug on the intestinal walls we carried out a series of experiments as illustrated in
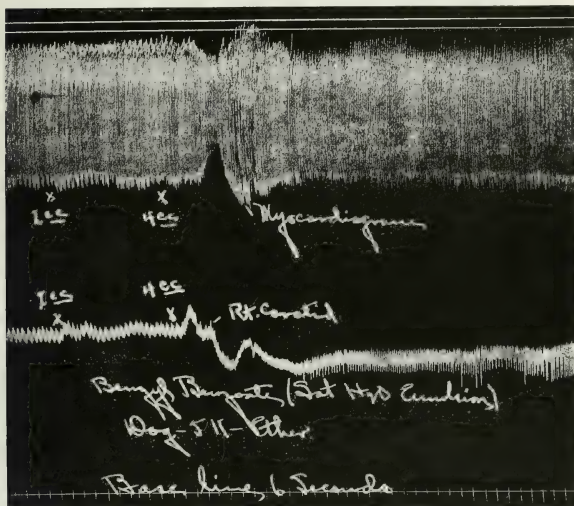
Figure 3.

Fig. 2. In this case a small rubber balloon (finger cot) filled with water was placed within the intestinal lumen and connected by rubber tubing with a burette which carried a stopper in the upper end. From the stopper a rubber tube led to the recording tambour. The water filled the balloon and reached about two inches up in the burette, the upper part of which was filled with air. Thus contractions which lessened the lumen of the intestine caused the writing point of the tambour to rise, and relaxation of the gut showed a fall in the kymograph tracing. In the beginning a small dose

(one half cc. of .5 per cent solution) of barium chloride was injected to stir up marked contractions of the intestine. The marked rise in tone of the intestine is well shown in the tracing. When the circular musculature of the gut was well contracted an injection of 2 cc. of benzyl benzoate was
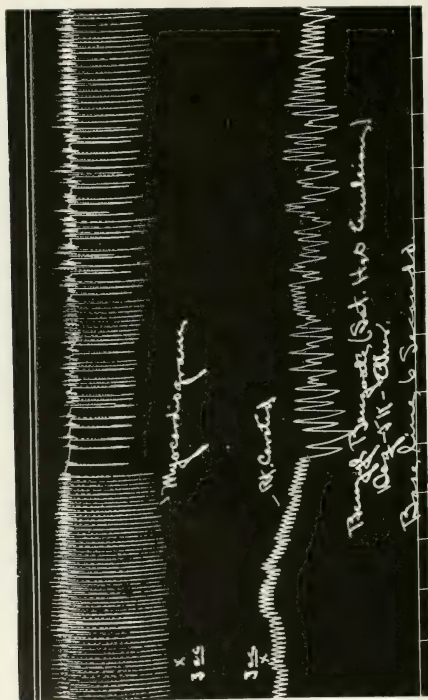
Figure 4

given. This depressed the respiration and slightly lowered the blood pressure, but produced no immediate change in the tone of the intestine. After an interval of about one minute, however, there occurred a relaxation of the intestine and at this point a further injection of 2 cc. of the drug

was given. This apparently slightly increased the tonus of the intestine and was followed by a series of small, irregular contractions. As a check on the technic of the experiment an injection of one-half cc. of adrenalin was
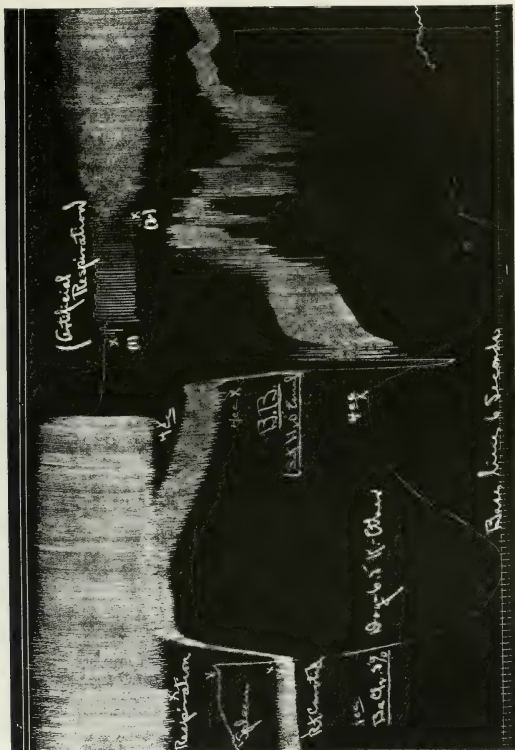
Figure 5.

finally given. This produced an immediate and complete relaxation of the gut. It will be noted that the second injection of benzyl benzoate greatly depressed the respiration, but both injections of benzyl benzoate taken to-

gether were very much less effective in lowering the tone of the intestinal musculature than was the one-half cc. of 1-10,000 adrenaline solution.

The injection of a sufficiently large dose of benzyl benzoate is followed by a prompt, pronounced and prolonged fall of blood pressure. From the

Figure 6.

nature of the blood pressure curve produced, we early conceived the idea that the heart played an important part in this lowering of the arterial tension. Figure 3 shows a tracing taken directly from the heart (upper curve; myocardiograph) and the right carotid pressure tracing. It will be noted that 2 cc. of benzyl benzoate gave little or no change, but that 4 cc. pro-

duced the characteristic fall in blood pressure. It is obvious that this fall in pressure is closely associated with the changes in the amplitude and force of the heart beat. But in order to analyze this point still further we present Fig. 4, in which the drum was made to revolve much more *rapidly* than in Fig. 3. Fig. 4 shows that 3 cc. of the drug was followed by a fall in blood pressure, but that the heart at the same time became weak and after
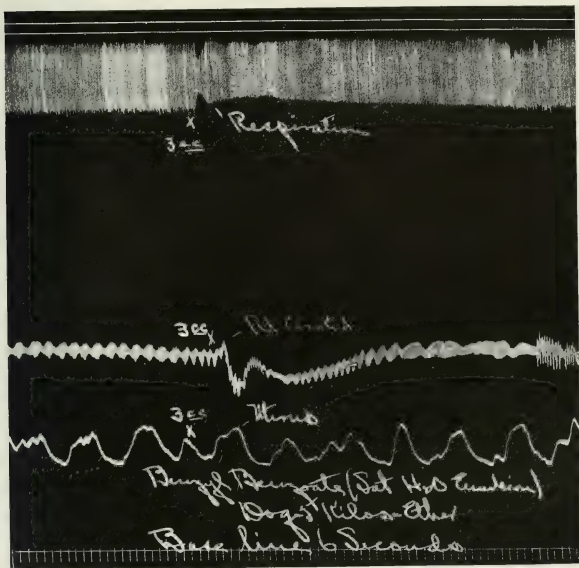
Figure 7.

an interval came near stopping in diastole. After a prolonged series of feeble, irregular beats, however, the heart again recovered slightly, and the blood pressure finally became somewhat more regular. These changes in the blood pressure are obviously due to a weakening action of the drug on the heart. It should be noted that this animal was receiving artificial respiration.

Fig. 5 shows the action of benzyl benzoate on the respiration, spleen volume and blood pressure of a dog weighing 6.5 kilos. In order to produce a

tonus in the spleen an injection of 1 cc. of .5 per cent. barium chloride was given at the beginning of the tracing. The contraction of the spleen became very marked and this was followed after a time by some relaxation. **Four c.c. of benzyl benzoate was now injected in order to see whether or not the drug would relax the spleen.** It will be noted that the spleen (oncometer) tracing again dips even lower than it did following the marked contraction produced by the barium chloride. But the causes of these two spleen contractions are, however, exactly the opposite of each other. In the first, the shrinkage of the spleen volume represents an *active contraction* of smooth
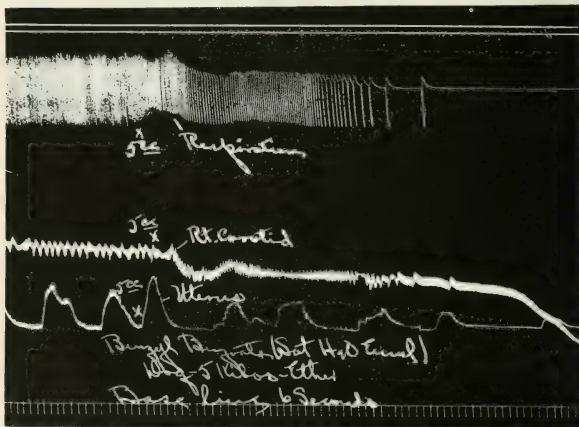
Figure 8.

muscle within the spleen. The second contraction is passive, and is due to the profound fall in blood pressure, and perhaps, somewhat to the asphyxia which followed the injection of the benzyl benzoate. Artificial respiration was started at "1" and stopped at "2." Although the blood pressure again returned to a high tension (continued action of the barium) and the spleen tracing also marked a low level (also barium contraction), still there is no evidence that the benzyl benzoate exercised any relaxing action on the spleen, although the dosage was perhaps sufficient to have killed the animal if artificial respiration had not been given. Under artificial respiration animals can withstand very much larger doses of the drug without dying, than is possible under natural respiration. This indicates that the animals do not

die of thrombosis as might be suspected from the rather unsatisfactory character of the drug for intravenous injection. The final recovery of the heart and circulation, if artificial respiration be maintained, shows that no permanent thrombi are lodged in any vitally important vascular areas.

Fig. 6 shows the respiration, kidney volume (oncometer) and blood pressure. In the beginning 4 cc. of benzyl benzoate solution was injected. Slight effects were produced in all three tracings. The small shrinkage in kidney volume is obviously secondary, and due to the fall in blood pressure. If the
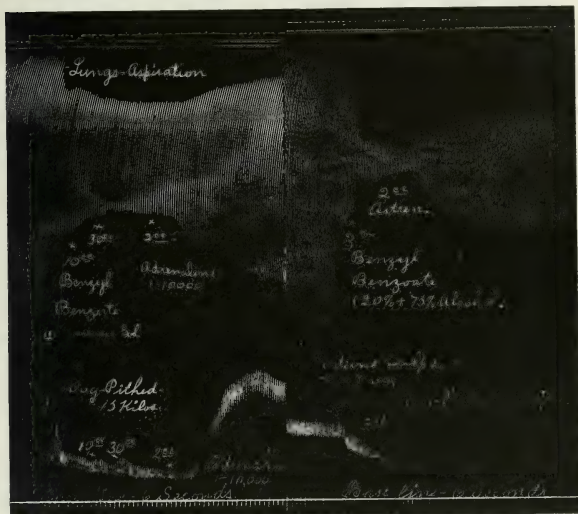
Figure 9.

arterioles themselves in the kidney had dilated the volume record would have risen, as occurs after the constriction produced by the 1 cc. injection of adrenalin (at the center of the tracing) begins to wear off. The shrinkage of the kidney volume after the adrenaline is active and is due to the adrenaline stimulating the myoneural junctions of the vasoconstrictor nerves in the renal arterioles. Following the adrenaline a further dose of 7 cc. of benzyl benzoate was given. The results of this were exactly analogous to those produced by the 4 cc., but were correspondingly more pronounced.

The recently suggested use of benzyl benzoate in clinical conditions presumably dependent on excessive or abnormal contraction of the uterus[3] indicated that the drug would probably produce relaxation of this organ. Figs. 7 and 8 show the results we have obtained in the study of the action of the drug on this organ. In Fig. 7 an injection of 3 cc. was made and
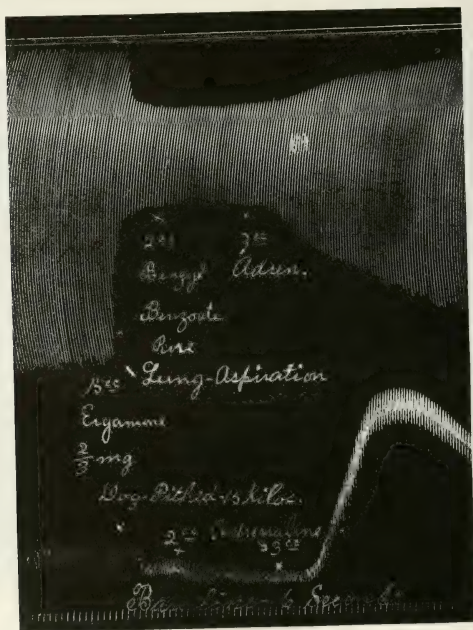
Figure 10.

produced very obvious results on the respiration and blood pressure. On the uterus, however, the results are very slight. Fig. 8 also shows the effects of an injection of 5 cc. of the drug. This dosage finally stopped the uterine contractions, but not until the animal had died. Obviously one could not use such large amounts clinically. In these tracings the uterus remained
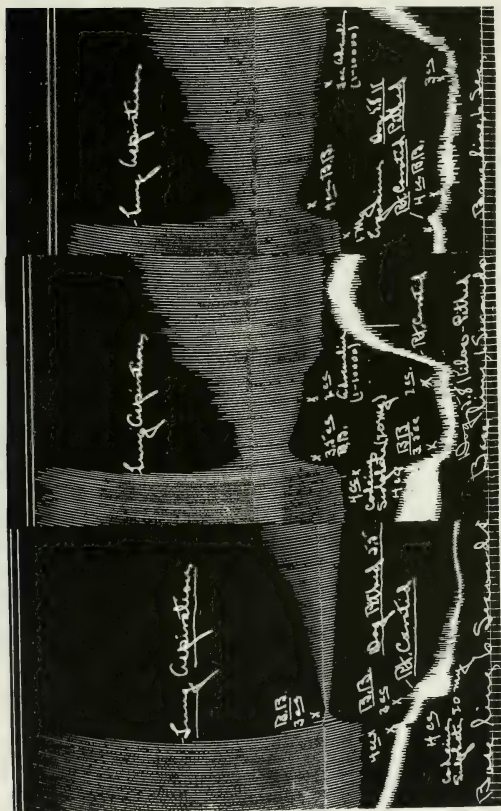
Figure 11.

in situ and great care was used not to disturb its innervation or blood supply, and to keep the organ warm and moist by closing the abdominal wall and covering the recording apparatus with the intestines (see Jour. Lab. and Clin. Med., 1917, iii, 63). In regard to these two records, however, it should
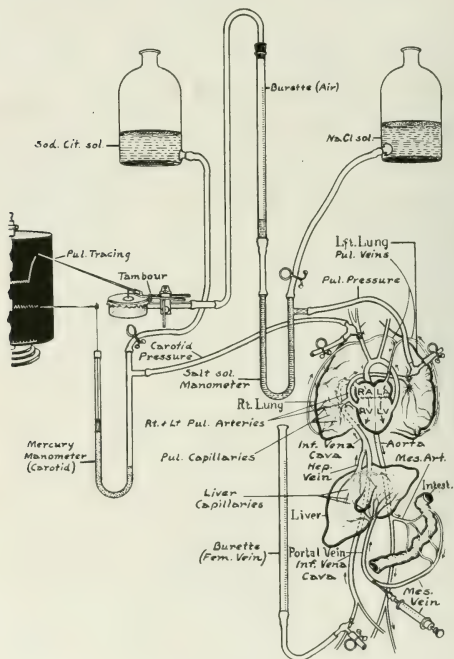
Figure 12.

be stated that it is often difficult to secure entirely satisfactory tracings of the uterus *in situ* in dogs, and we should not be inclined to lay too great emphasis on these observations without checking the results by a considerable number of experiments on animals of different species, which we have not

as yet had an opportunity to do. In our present experiments the uterus had previously been roused to increased activity by the injection of pituitrin.

One of the most important clinical uses suggested for benzyl benzoate is in the treatment of bronchial asthma.[4] Fig. 9 represents two tracing taken from separate dogs and mounted together. They show the action in spinal dogs of histamine (B-iminazolylethylamine, "ergamine"), benzyl benzoate, codeine and adrenaline on the bronchioles as recorded by a special aspiration method (see Jour. Pharmacol. and Exper. Therap., 1914, vi, 57; also,
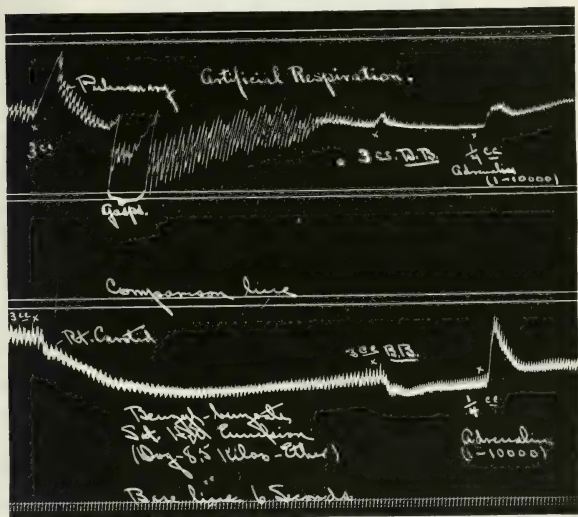
Figure 13.

Jackson's Experimental Pharmacology, C. V. Mosby Co., 1917, St. Louis, p. 287). In these tracings (also Figs. 10 and 11) a shortening of the amplitude of the lung record means contraction of the bronchioles, and increase in the amplitude of the lung tracing shows dilatation of the bronchioles. In Fig. 9 the left hand record shows a contraction of the bronchioles produced by the intravenous injection of two-thirds milligram of ergamine. This led to a bronchial contraction which 10 cc. and, later 30 cc. of an aqueous solution of benzyl benzoate did not relax. An injection of adrenaline (2 cc.)

produced prompt bronchial dilatation. In the right hand tracing codeine was used to produce the initial bronchial contraction and then 3 cc. of the 20 per cent. benzoate made up in 75 per cent. alcohol was injected intravenously.
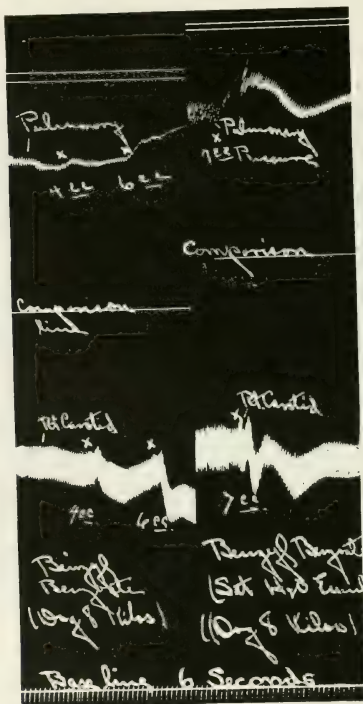
Figure 14.

The dog weighed 8 kilos and it would appear that this dosage should certainly have caused dilatation of the bronchioles. This did not occur, however, and as a further check on the technic of the experiment 2 cc. of adrena-

lin was injected. A bronchial dilatation followed although the heart stopped beating (from the effects of the codeine and benzyl benzoate). Fig. 10 shows that 2 cc. of *pure* benzyl benzoate (made by the Harmer Laboratories) did not produce the slightest indication of a bronchial dilatation following a contraction produced by "ergamine." Adrenaline, however, caused a marked dilatation. This seems to indicate definitely that benzyl benzoate does not cause a bronchodilatation in intact (pithed) dogs under the conditions obtaining in such experiments as we have here carried out. Fig. 11 shows three separate tracings mounted together. From the legends it will be seen that benzyl benzoate did not produce satisfactory bronchodilatation in either instance.

The possibility that benzyl benzoate might be used clinically in pulmonary hemorrhage in cases of tuberculosis led us to investigate the action of the drug on the pulmonary blood pressure. The method we have used for recording the pulmonary arterial pressure is indicated in Fig. 12. (See Jour. Lab. and Clin. Med., 1920, vi, 1). In the diagram it will be seen that a cannula tied into the left pulmonary artery connects with a water manometer, the distal end of which is joined to the lower end of a burette. The manometer and tubes to the artery (and the cannula) are filled with normal salt solution. The upper end of the burette is connected with a recording tambour which writes on the drum. The tambour, the upper part of the burette and the connecting tubes are filled with air. By this method the pulmonary blood pressure record represents a magnification about 150 times greater than would be recorded by a mercury manometer. The variations in the pulmonary tracings should, therefore, be reduced about 150 times in amplitude in order to compare them directly with the associated carotid tracings which, in our records, were made with a mercury manometer. Fig. 13 shows the results we have observed on the pulmonary arterial pressure. Near the beginning of the tracing 3 cc. of benzyl benzoate was injected and a typical, prolonged fall in the carotid pressure was obtained. In the pulmonary pressure, however, there was produced at first a sharp temporary rise which was succeeded by a few gasping movements. But on the average there was extremely little variation in the pulmonary pressure, either in the way of a rise or a fall. Later a 3 cc. injection of benzyl benzoate was given again. The fall produced in the carotid pressure was again quite typical, but the pulmonary pressure showed only a very slight, transient rise. A small injection of adrenaline was finally given in order to check up the accuracy of the technic in the experiment. Fig. 14 shows two short pulmonary tracing (mounted together). Here again the drug produced only the slightest changes in the pulmonary pressure. In studying these tracings one must, of course, constantly bear in mind the greatly increased magnification of the pulmonary over the carotid records. It is obvious that if the drug should act in clinical cases in a manner at all analogous to that in

which it has behaved under these experimental conditions, it could be of no use in the matter of treatment of hemoptysis in pulmonary tuberculosis.

REFERENCES.

1. Macht, David I.: Jour. Pharmacol. and Exper. Therap., 1918, xi, No. 6, p. 421.
2. Macht, David I.: Jour. Am. Med. Assn., August 23, 1919, pp. 599-601.
3. Litzenberg, Jennings C.: Jour. Am. Med. Assn., August 23, 1919, pp. 601-603.
4. Macht, David I.: Southern Med. Jour., July, 1919, xii, No. 7, p. 367.

RELATION OF THE DEVELOPMENT OF THE GASTRO-
INTESTINAL TRACT TO ABDOMINAL SURGERY.*

W. J. Mayo, M. D.

Rochester, Minn.

THE RELATION OF ANATOMY TO PRESENT DAY SURGERY.

The late Corydon L. Ford, professor of anatomy at the University of Michigan Medical School, was justly considered the greatest teacher of anatomy of his time. I well remember the three years in which I studied anatomy under him, and the impression he made on the students by his clear and forceful presentation of this ordinarily dry subject. He was then a man past middle life; he wore a beard, shaved the upper lip, and because of a congenital clubfoot he walked with a decided limp by the aid of an ivory-headed cane. I speak of these physical factors because they were part and parcel of the man in relation to his teaching. He presented anatomy not alone as a fundamental science which it was necessary to master for the purpose of laying a foundation for clinical medicine, but as a living thing to be considered in almost every professional act. He was then closely in touch with the clinical issues of his time, and with anatomy he taught most valuable lessons in physiology and pathology, so that the student gained knowledge of his subject in its relation to his work. The university courses in surgical anatomy were excellent, yet Ford taught us more surgical anatomy than we learned in these special courses, and he also taught us medical anatomy. in order that we might see the patient from the anatomic standpoint, and recognize pathologic deviations from the normal in the early stages. We were drilled in the use of Holden's "Anatomical Landmarks"; I have spent many hours with this little book, going over the living body that I might learn the relation of the external to the internal.

As volunteer assistant I had the further privilege of demonstrating anatomy at the University of Michigan, and the fascination for anatomic detail in relation to medicine and surgery has remained with me. My seat companion was the late Franklin P. Mall, afterward professor of anatomy at Johns Hopkins, and the most distinguished anatomist of his time. Mall was a choice spirit, an anatomist of the research type. On one occasion in showing me the manner in which the heart, by its peculiar twisting contraction, empties all the blood from its cavities as one would wring a cloth, he remarked that a cavity like the bladder cannot empty itself to the last drop by contractions alone. He said that anatomy since Ford's time had dealt too much with abstract matter. Mall's observation has an important bearing on catheter cystitis, an infection of a small amount of residual urine in an overstretched organ.

During my active experience in surgery, working with many different assistants, I have not always been impressed with their knowledge of anatomy, although all have possessed a fair knowledge of pathology. At times it would seem that they were more familiar with minute pathology than with anatomy. Microscopic histology and pathology, while not overdone, have been allowed to overshadow anatomy and gross pathology—these the surgeon or internist must see with his own eyes if he is to do his best work. It is a question in my mind whether, generally speaking, anatomy is as well taught today as it was in my student days; whether it is taught with a view of instilling in a man a love for the subject, or merely as a foundation for medical practice. I believe this tendency is correctly interpreted by teaching anatomists of the type of Jackson and others, who are taking steps to remedy the existing defects by the better balancing of anatomic teaching. This is also true of the teaching of present day pathologists.

In surgery of the abdomen especially, a wide knowledge of embryology and anatomy is essential. In the olden time when operations were done in late periods of pathologic conditions, and were destructive rather than reconstructive because it was necessary to save life and it was too late to save function, one could fully appreciate the answer of the distinguished surgeon who originated excision of the hip when asked concerning the anatomic details of the operation: "Damn the anatomy; stick close to the bone." Today the bulk of surgery is not done for gross defects but for pathologic conditions which have not deviated from the normal to such an extent that destructive surgery is necessary, but are still in condition for reconstruction. It has been said that the anatomist never made a good surgeon: that it was the pathologist who made the surgeon. This is true only of the vanishing German type. The surgeon of tomorrow must follow in the footsteps of such men as Deaver; he must be an anatomist and a physiologist, and living pathology must hold a greater place in his mind than the pathology which has been developed from the mortuary and has dominated medicine for the past generation.

For many years I have been interested in elucidating problems of surgery of the abdomen. Clinical diagnosis has been notoriously unreliable, and the postmortem does not show the chronic disease from which the patient was sick during life, but rather the particular complication from which he died. Always, when I have faced a new problem in this field, I have gone back to embryology, anatomy and physiology in order to gain an idea of the meanings of those pathologic deviations which we are called on to treat. It may not be out of place at this time to outline sketchily some of the anatomic and physiologic principles that have grown up with the surgery of the abdomen, and on which depends the explanation of many phenomena that could not otherwise be understood.

From the time the food passes through the pharynx until it enters the rectum we have comparatively little control over it. Some control is exercised in the esophagus and even in the fundus of the stomach so that by

initiating retrograde movements, retching, and so forth, some food may be ejected. The same is true in the sigmoid; but even in it the control at best is but partial and indirect. The biologists have pointed out that the theory of the three blastodermic membranes is a working rule and not a law, having many exceptions; but at least it leads to logical thought. To a certain extent this is also true of the idea of the derivation of the gastro-intestinal tract from the fore, middle and hind guts. Yet these primitive derivatives, while not as exact in the present day human body as might be desirable from a purely scientific point of view, have great value as outlines for the student.

From the foregut come the stomach, the duodenum down to the common duct, the liver and the pancreas, all organs which prepare food for digestion but do not themselves absorb. The stomach does not absorb even water, although it will take up certain chemicals and poisons, alcohol, for instance. The derivatives of the hindgut likewise absorb nothing except certain chemical substances, and rectal feeding, as spoken of in its ordinary sense, does not exist: it is simply a means whereby material placed in the rectum is quickly carried by what Bond calls "mucous currents" back into the derivatives of the midgut for absorption. The so-called colon tube passes out of sight through the anus, coiling in the rectum, and but seldom passes the rectosigmoid barrier. The derivatives of the foregut have their blood supply from the celiac axis. The derivatives of the midgut, in which absorption takes place, are supplied from the superior mesenteric artery, while the inferior mesenteric artery supplies the derivatives of the hindgut as far down as the rectum, and very largely the rectum also, although the rectum and anal canal obtain a small supply from the middle and external hemorrhoidals because of their origin from the cloaca and the protodeum.

Rosenow's work on the specificity of bacteria shows the bacteria that have been cultivated in certain soils, in the gallbladder, for example, when placed in the circulation, are peculiarly attracted to the organ to which they have been acclimated. That is, strains of bacteria derived experimentally from a gallbladder will more often set up a cholecystitis than if they were derived from some other organ. This is true along so many lines connected with the vascular system that we must admit at least the possibility that the blood supply is to a certain extent specific and that organs exercise some peculiar chemotaxis which physiologically and pathologically directs certain substances of the blood content to them. How else can we explain the rapidity with which phenolsulphonephthalein is eliminated through the kidneys? And recent work in physics suggests that the attraction may be a physico-chemical one. Very delicate instruments appear to show that each organ has its own electrical reactions and polarity, suggesting that cancerous growths can be recognized in this way.

Embryologically the first portion of the duodenum ends, not at the pylorus but at the common duct, and the duodenum above the common duct embryologically is a part of the stomach and a vestibule to the small intes-

tine; like the stomach and other acid-containing organs, it is extremely liable to ulceration. Ulcers of the duodenum occur more commonly in men than in women, possibly because the first portion of the duodenum in women is more nearly horizontal, naturally permitting of a higher alkaline level for the bile and pancreatic juice, and thereby reducing the liability to ulceration. In animals with bilocular stomachs the division between the two stomachs is at the incisura of the human stomach, and the physiologic activity of the pyloric half of the stomach, especially at the incisura, is quite evident on roentgen-ray examination, although the musculature composing the primitive sphincter has disappeared.

The termination of the absorbing intestinal area in the transverse colon near the splenic flexure embryologically marks the end of the absorbing area. It is interesting to note that, although the proximal half of the large intestine has no marked anatomic differences from the left half, in the embryo villi are to be found in the right half which are similar to the villi of the small intestine, although they disappear as development proceeds. An observer, watching with the roentgen ray the churning back and forth in the head of the colon sees that the greater part of this activity is proximal to the location of the cecocolic sphincter which exists in the ascending colon of some of the lower animals, and that physiologic contractions are most marked in this situation. Retardation of the passage of food through the intestinal tract has its origin in embryologic physiology. Muscular control by means of sphincters, delay by means of the valvulae conniventes which also present larger exposed surfaces for absorption, delay by sacculations, as in the large intestine, and mechanical delays, such as the high attachments of the splenic flexure which necessitate muscular activity in order to pass the food refuse into the nonabsorbing part of the large intestine and render the descending colon physiologically empty, are examples. The rectosigmoid is a most remarkable mechanical device for retardation of food end-products. Since nature is most sparing of waste, even of water, in the terminal half of the large intestine, especially the sigmoid, the fluids are gradually squeezed out of the refuse and passed by reverse currents back into the proximal half of the colon for absorption.

Rotation has great surgical significance. In the embryo and in many lower animals throughout life the stomach hangs with its lesser curvature facing ventrally; and embryologically the lesser curvature is the anterior wall of the stomach. Rotation turns the stomach and pancreas on their right sides. The pancreas, embryologically an intraperitoneal organ, loses its posterior layer of peritoneum, which becomes fused behind with the fascia. This explains why, in the type of acute pancreatitis and fat necrosis which might be picturesquely called "perforation," the pancreas may involve the fat behind the peritoneum as well as the intra-abdominal fat; why occasionally, in traumatism, pancreatic secretions escaping into the lesser cavity of the peritoneum may penetrate into the omentum and form a collection of fluid in what is known as the omental bursa, reopening the

cavity which in fetal life exists between the layers of the omentum before they are fused as high as the transverse colon.

The position of the duodenum is altered by rotation and its third portion becomes retroperitoneal, a fact of great importance in connection with operations on the right kidney. Unless care is exercised in performing a nephrectomy in cases in which there is chronic inflammation around the pelvis, and especially in malignant disease, the duodenum may be injured, and immediately or a few days later a fistula form from which the patient may die unless it is repaired anteriorly by a transperitoneal operation. Very scanty mention of this accident is found in the literature, but I have reported several cases of this character. Unless careful dissection is made, this retroperitoneal portion of the duodenum also may be injured in the removal of cancers of the ascending colon.

Rotation as it affects the intestinal tract is also of great surgical importance. The large intestine, having its origin on the left side of the body, passes to the right and does not reach its normal situation until after birth. The late peritoneal attachments are often described as veils or adhesions, and are given unwarranted credit for causing trouble. Failure of rotation or partial rotation will cause the physical signs of an appendicitis to appear at whatever point the rotation of the head of the colon is interrupted. The attachments of the large intestine to the right side are not only late and less close than those on the left, but also, since the cubic capacity of the right lower thorax is less than that of the left lower thorax, because of the liver, the right kidney normally lies lower than the left. The nephrocolic ligament may be called on to bear much of the weight of the head of the imperfectly attached colon which acts like the car attached to a balloon, and may, by traction, drag the kidney down. We think of the large intestine as having a short mesentery; but as a matter of fact, it has a very long mesentery on the inner side, which is the only side of importance, as the blood vessels, lymphatics and nerve supply are always to be found in the inner long leaf which follows the colon during its migration. The outer peritoneal attachments which hold the colon in place laterally may, therefore, be divided without encountering any structures of importance, and the large intestine, on its long inner leaf of mesentery, can be drawn out of the body for easy manipulation and operation. There is one exception; that is, the attachments of the splenic flexure are derived from the omentum and contain a blood vessel which must be tied. Some years ago I called attention to this method of mobilizing the large intestine, which is based on these anatomic facts and very greatly aids in operations on the colon.

The small intestine, originating in six primary convolutions on the right side, has its mesenteric attachment from left to right, from above downward, passing behind the umbilicus. This is the reason why in obstructive and other disturbances of the small intestine, unless localized by involvement of the peritoneum, the pain is referred to the vicinity of the umbilicus, although the cause of the pain may be in a loop of intestine at a distance.

In picking up a loop of small intestine, it is sometimes difficult to determine which direction is up and which is down. Monks, in a beautiful piece of work, has shown how this can be done with facility. If a loop of intestine drawn out of an abdominal incision is held by an assistant, and the surgeon, grasping the intestine with the fingers on one side and with the thumb on the other, passes down to the bottom of the mesentery, and finds that his fingers and thumb still grasp the root of the mesentery as started above, the direction is up and down; but if the position is reversed at the base, then the direction is the opposite. In picking up a piece of small intestine one should be able to recognize the part of the bowel from its appearance. The upper jejunum is thick and wide, the mesentery is thin, and the vessels are large, long and straight, having but one or two primary arcades close to the base. In the lower ileum the intestine is thin and the mesentery thick, the fat sometimes following the vessels a little way up along the intestinal wall. The vessels are smaller, shorter, and there are a number of arcades, sometimes two, three or four, in the adjacent mesentery. Attention to these details makes ready differentiation possible.

The study of the peritoneum is profitable to the surgeon. The resistance of the peritoneum to infection is an inherited faculty. The meninges and pleura have less resistance. In the earthworm (common angleworm), the food, in its progress through the primitive gastro-intestinal canal, is admitted into the coelom, or body cavity, which is the forerunner of the peritoneum, for direct absorption. The contaminated peritoneum before infection takes place usually needs no drainage after mechanical cleansing; drainage often does harm rather than good. The slowly acquired special resistance of the pelvic peritoneum of women to infections in the course of countless generations of suffering from puerperal and other infections, is well known; and the mortality rate of operations involving the pelvic peritoneum, such as resections of the rectum for cancer, is much less in women than in men.

Let me repeat that the teaching of anatomy, as related to constructive surgery rather than to the destructive surgery of the past, should be based on the needs of the surgeon of today, to enable him to cope with the diseases of today. If I were to write a book (I have no intention of inflicting one on the medical public), I should take up the fascinating story of embryology, anatomy and physiology in relation to the work of the surgeon of tomorrow, the story of the anatomy of the living to enable us to treat the pathology of the living during the early stage of deviation from the normal physiologic state.

CO-ORDINATION OF THE FUNCTIONS OF THE GASTRO-INTESTINAL TRACT

The two most primitive functions of a living body are maintenance of nutrition and reproduction, and nature has thrown about these functions the greatest possible number of safeguards. First, the body must be nourished, and second, new life is to be brought into being. This is as true of the

simple cell as of the most complex organism. The more ancient the organ, the greater its resistance. The small intestine has an enormous resistance to disease and seldom is the seat of neoplasm. The testicle, which is the primitive reproductive organ, has a long heredity and freedom from disease. On the contrary, the ovary, which is descended from the testicle, is, like other less ancient organs, such as the stomach, the rectum and the large intestine, a frequent seat of neoplasm.

Methods of control over the visceral functions were established before man had a central nervous system; these controls are still independent of it. It might even be surmised that the attempt of the central nervous system to gain control over visceral and other functions previously established may have to do with neurasthenia, especially its visceral manifestations. Starling well says that those internal secretions, which he calls hormones, precede all types of nervous systems in visceral control. One is perhaps justified in looking on the sympathetic as the more primitive nervous system and in believing that the means whereby the central nervous system is attempting to gain this control over the vegetative functions is through the autonomic nervous system.

The liver, entirely separated from all its connections, can be made to secrete bile, and the kidney similarly to secrete urine. For that matter, the entire viscera have been completely separated experimentally from the nervous system and even lifted out of the body, and by appropriate mechanical connections made to live and function for some hours. The central nervous system, we find, has more or less control of those organs which have been added more recently, especially organs of convenience, such as the fundus of the stomach, into which a quantity of food may be placed rapidly for elaboration, as the magazine of a coal stove may be filled. The sigmoid and the bladder also have temporary storage function; but in other respects the central nervous system, beyond initiating action, plays a small part in vegetative life.

The growth of the central nervous system in relation to the organs of special sense is interesting. First, the sense of taste, which made the selection of food possible; second, the sense of smell, which enabled the primitive stoma to be turned toward food, and third, the sense of hearing, which was placed in the middle of the head because danger threatens from behind as well as in front. The sense of sight came during the rapid development of all the higher cerebral faculties, and direct pathways were established between the eye and all parts of the brain, so that the sense of sight overshadows in importance the other special senses. Even memory in most persons has its basis in visual phenomena. The relatively short heredity of the central nervous system accounts for its instability.

It is interesting to note that the sympathetic nervous system is in close relation with the endocrine glands, and that the importance of the internal secretion of an organ may be estimated by the closeness of its relation to

the sympathetic system. The pituitary, one-half sympathetic and one-half gland, the suprarenal, with its similar association, and the thyroid, are examples; the spleen has no internal secretion of great importance, and only small connection with the sympathetic system.

Still another form of control is found in the primitive character of the nonstriated muscle. These fibers have the power of originating motion independent of a known nervous system. A little piece of the wall of the small intestine will contract for hours when placed in Locke's solution and properly stimulated. Many visceral functions are dependent on the nonstriated muscle. We are indebted to Keith for revelations with regard to the curious nodal system which acts to collect the impulses that have their origin in the primitive fibers of the nonstriated muscle. This has been most carefully studied with reference to the heart. The heart-beat starts in the sinu-auricular node, is diffused through the auricular musculature, and is passed by the muscle-band of His to the vetricles, timing the ventricular beat. Keith's nodes are composed of a curious type of primitive muscle-cell with some fine fibers from the autonomic nervous system which evidently were added later. These nodes are in effect the controlling ganglions of the action of the nonstriated muscle in organs. Keith has pointed out the situation of eight nodes, four located and four not fully identified, through which control is maintained. When food passes through the pharynx, all direct control is at once lost, and here is situated the first node. The cardia is a true sphincter and normally is closed. The food passing through the esophagus arouses contractions in the nonstriated muscle of the esophagus; these impulses are carried to the second node, which relaxes the cardiac orifice. Failure to relax the cardiac orifice results in that curious condition called cardiospasm from which many persons suffer and starve for years, and often die from obstruction supposed to be due to cancer. If we have knowledge of the nature of the disease, cure is easy and certain. The third node is not at the pylorus as one would think, but at the termination of the primitive foregut near the common duct. It is interesting to note that, as pointed out by Ochsner, there are remnants of a prehistoric sphincter at this point. Disturbances of this node produce the condition called pylorospasm, which accounts for many gastric disturbances masquerading under different names. This node is also concerned in chronic gastric atony and some of the phases of acute dilatation of the stomach. The fourth node is near the duodenojejunal juncture and is concerned normally in peristalsis and in segmentation or pendulum movements of the small intestine, and abnormally in producing gastromesenteric ileus. The fifth node is at the ileocecal juncture and is concerned with many of those phenomena about which Lane has written so interestingly under the general head of ileac stasis. The sixth node is near the middle of the transverse colon, and through its control of antiperistalsis prolongs the retention of food products for absorption in the right half of the colon. The

seventh node is in the rectosigmoid region, and disturbances in the function of this node are probably responsible for the giant colon of Hirschsprung's disease. The last, or eighth, node is concerned with rectal control.

It may be said that wherever nonstriated muscle exists, the power of originating contraction exists. The intestine, like the heart, has two beats. The first, called the peristalsis, beats once or twice to the minute. The second, as pointed out by Mall, is the heart of the portal circulation and beats from eighteen to twenty times a minute, forcing the blood to the liver. In the pregnant uterus, the beat of the nonstriated muscle is recognized as the uterine contractions of pregnancy. Keith points out the part played by the nodes in controlling peristalsis, and suggests that they act like a block system on a railroad, and control food progress by controlling sphincters.

The endocrine glands secrete substances which Starling has called hormones; they act through the blood stream and form a most interesting chapter in visceral control; they are closely allied to the sympathetic nervous system, and are often found in glands of double function or glands that at one time have had an external as well as an internal secretion. The gonadial secretion derived from the interstitial cells of the generative organs controls sex characteristic even when the genital elements are absent. The relation of the external pancreatic secretion dealing with the digestion of fats, starches and proteins has only an indirect connection with the tissue of Langerhans, which has to do with sugar metabolism. The thyroid in the king scorpion is a reproductive gland, and the thyroid function in the human being is closely connected with puberty, in the female, with the pregnant state. Types of life are found in which the thyroid functioned through the digestive tract, and the foramen cecum at the base of the tongue in man marks the site where this secretion was at one time discharged into the intestinal canal. In the present stage of human development, the thyroid is entirely an organ of internal secretion; but through its influence on other endocrine glands, it assists in maintaining reproductive and digestive functions.

The pituitary gland probably corresponds to the strainer gland in the fish stage, and in the course of development was left within the skull instead of on the side of the pharynx. It contains elements derived from the pharyngeal mucosa, and many of its tumors show pharyngeal heredity. Is it possible that this gland, which is so important in the growth of the body, is favorably affected through improved circulation by the removal of diseased adenoids and tonsils? Certainly one often sees a child of slow development, after an operation for removal of tonsils and adenoids, make a most striking physical and mental gain. The coccygeal body (gland of Luschka) has no known function, but it is connected with that stage of development in which the primitive hind or tail gut was part of the neurenteric canal. These prenatal vestiges may be the source of dermoids or neoplasms of peculiar na-

ture, not infrequently malignant, lying in the hollow of the sacrum behind the rectum and eroding the bone. Some theorists have called the external vestigial remnants of the neurenteric canal the posterior umbilicus, and believe that the sequestration dermoids so frequently found in the lower sacral and coccygeal midline have this origin. Keith points out that the internal secretions of the five important endocrine glands,—pituitary, suprarenals, gonadial, pineal and thyroid, control racial characteristics of the three great divisions of man, Caucasion, Negro and Mongol.

The sympathetic nervous system was a later development, and correlates visceral action. It stimulates the function of endocrine glands, and is in turn stimulated by their secretions. To the great English physiologist Gaskell we owe our knowledge of the involuntary nervous system. His first work on the visceral nervous system was published in the early eighties. Gaskell pointed out that certain small-calibered medullated nerves pass from the anterior horns of the spinal cord to the great sympathetic ganglion of the thorax and abdomen, which connects the central nervous system with the sympathetic. These connecting nerves enable emotions originating in the central nervous system to influence the sympathetic ganglion. From the sympathetic ganglion small nonmedullated fibers pass directly to their distribution forming the sympathetic nervous system. Gaskell also showed that there are nerves of the same kind which have visceral functions arising from the cranial nerves, and he called these para-sympathetics. They are composed of the vagus nerve, the fibers in the third, seventh and ninth cranial nerves, and the pelvic nerve from the sacral plexus. The para-sympathetics are small-calibered medullated nerves with ganglion cells near their distribution, as in the heart itself and in the plexuses of Auerbach in the wall of the intestine. Neither the sympathetics nor the parasympathetics are under the control of the will, and when distributed to the same organ they follow Sherrington's law in that they are antagonistic.

Langley, who contributed much to this work, called the combined sympathetic nervous system (thoracic and lumbar ganglions) and the parasympathetic (cranial and pelvic) the autonomic system. American physiologists, especially Cannon and Crile, have contributed largely to this work. Gaskell pointed out that the sympathetic ganglions develop widespread reactions to stimuli which exercise inhibitory control over the vegetation system independent of the will, and inhibit the parasympathetics. The cerebrospinal nervous system produces a conscious and accurate action of the striated muscle system, but has no control, and only indirect effect, on the nonstriated muscles. Langley, Crile, Cannon and Brown have made practical application of Gaskell's discoveries, showing how the fibers derived from the sympathetic ganglions, acting for defense, produce the most widespread and sudden effect when excited by emotions such as fear or anger. The digestive tract is temporarily deprived of function; the heart action and respiration increase in rapidity and strength, the glands of internal secre-

tion, especially the suprarenals and thyroid, are activated, and sugar reserves in the liver and body generally are thrown into the blood stream to enable greater muscular action.

It is interesting to note that the nerves of Gaskell from the anterior horns of the spinal cord to the sympathetic ganglions are direct, and it is only those nerve fibers derived from the sympathetic ganglions themselves that pass to the various organs to produce the widespread effects spoken of, with the exception of the suprarenal gland, which receives fibers from the cord en route. The suprarenal contains within itself true nerve cells, as though at one time a start had been made for a different type of control from that which was afterward developed through the sympathetic ganglions. The parasympathetics of Gaskell, as related to the gastro-intestinal viscera, are composed of the vagus nerve derived from the bulbar division of the parasympathetics, and the pelvic nerve from the sacral plexus. When the emotions, which, acting through the sympathetic system cause the sudden necessity for instantaneous use of all the body reserves, have passed away, the vagus nerve comes into action and causes the heart to beat more slowly, and reduces respiration. The digestive tract, the stomach, intestine, liver and pancreas, which have been temporarily inhibited by the sympathetic fibers from the solar plexus, are stimulated to function through the vagus parasympathetic acting as a motor nerve through the plexus of Auerbach, and the pelvic parasympathetic motor nerve again permits conscious control of the bladder, sigmoid and rectum, which had been inhibited by the sympathetic fibers from the inferior mesenteric ganglion. One may well believe, however, that while these functions are checked by the sympathetic and are caused to resume action by the parasympathetics, control of their normal activities goes back to the nonstriated muscles, and the internal secretions which were the earliest forms of control. The gastro-intestinal tract is, therefore, largely controlled in its functions by the nonstriated muscle and by chemical substances acting through the blood. The sympathetic ganglions act to inhibit these functions temporarily to produce rapid catabolism and spend reserves prodigally. The parasympathetics set in motion the interrupted anabolic activities and maintain reserves for future emergencies.

It may seem that these well-known anatomic and physiologic details need no reiteration, and yet in my association and teaching of younger men in the profession I find that while they may know these facts, they often fail in their interpretation of them. The interpretation of the interesting phenomena which I have cited may not be correct in given instances; but if by "near-right" theories a dry subject may be made to live, the means will be justified and the strain on our memories will be less. We must not forget that memory training is the Confucian method which certainly has not led the Chinese in the paths of progress. Facts do not change. The interpretation of facts constantly changes, and new interpretations of old and new facts are the source of progress. Only as we are doubtful of our interpretations can we hope to advance scientifically.

THE NECESSITY FOR THE APPLICATION OF DIFFERENTIAL AIR-PRESSURE IN THORACIC OPERATIONS.*

WILLY MEYER, M. D.

New York.

For the second time the annual meeting brings together the members of the American Association for Thoracic Surgery.

This young organization, embracing members of the medical profession who are interested in the study of diseases of organs situated within the chest, saw the light of day at the time of the meeting of the American Medical Association in New York City, on June 9, 1917, and celebrated its first birthday in Chicago on June 9, 1918.

It would be difficult to begin this second meeting better than by repeating the words with which the first, amidst a rising vote of thanks, was closed: "Our Association is proud and gratified to have it spread on its minutes that Dr. S. J. Meltzer, the renowned physiologist and internist, the man who has done so much for the evolution of thoracic surgery, was its first president."

If I might speak my inmost thoughts, I would say, I should have felt happy had there been no successor, and had Dr. Meltzer adorned the presidential chair for another year, nay, for life. But he willed it otherwise; and so, gentlemen, by your kind choice, I stand before you as your presiding officer. Let me thank you most sincerely for the honor and your trust; they are highly appreciated.

The task of finding a topic for the time-honored presidential address has been made easy. Within the last year we have had new proof that the usefulness of what I consider the *very foundation of modern thoracic surgery,* viz., the principle of employing "differential air-pressure" in the course of our operative work within the thorax, has not yet been generally recognized in its importance as a life-saver.

Hence, it appears to me appropriate that I should devote this address to a discussion of the place occupied in thoracic surgery by differential pressure apparatus, using the words in their widest sense, *i. e.,* including all such apparatus and methods as we know of. In again calling attention to the necessity of their use in thoracic operations, I feel certain to be voicing not only my own personal opinion, but to be putting on record the sense of the majority of surgeons in this Association.

Let us see just what does occur when a healthy parietal pleura is perforated. Which are the symptoms and sequelæ of the acute pneumothorax? Which are the physical and pathological conditions surrounding it.

"Observing a deeply narcotized dog, whose pleura has been incised in experimental surgery, a very typical and characteristic clinical picture will be seen to develop. Immediately after the opening of the pleural cavity and the subsequent prompt retraction of the lung, a brief cessation of the respiration occurs by reflex. This is followed by sudden, almost projectile attempts at inspiration and expiration. The entire accessory muscular apparatus is called into strenuous action. The thorax moves up and down over the collapsed lung which is seen lying immovable in the depth; its originally glistening surface has assumed a congested appearance, and its normal pinkish color has given way to a dark grayish-red. Soon the frequency and the depth of the respiration increase, as may be observed by watching the excursions of the chest wall. At the same time the respiration becomes irregular. After a few minutes the symptoms are less stormy, the respiration becomes quieter and more regular, but slower and deeper than under normal conditions. This slowing up of the respiration, which gradually increases, is produced by the lengthening of the expiratory phase. A little later only brief inspirations occur at longer intervals. Soon the respiration, and therewith, the heart's action stop completely." (Sauerbruch.)

Experiments further show that when both pleural cavities of the dog are simultaneously opened, respiration soon ceases, subsequent to most violent efforts of nature to hold back the waning life by means of very deep inspirations and expirations. Death occurs by suffocation.

In unilateral acute pneumothorax in the human subject, the disturbance is frequently less pronounced than in the dog, though it varies widely in severity in different individuals.

For the alteration in respiration various causes are responsible.

The principal rôle is played by the mediastinum. The anatomical organs and parts composing the mediastinum divide the thorax into two compartments, which latter are completely filled with lung. With the exception of the heart and large blood vessels the greater part of the mediastinal tissues represent a soft yielding mass, in which very little resistance to lateral pressure is offered.

Under physiological conditions the perfect equality of forces existing in the chest on both sides of the mediastinum keep the contents of the latter in their normal position of rest. The part of the pleural sac that lines the mediastinal structures, chest wall, and diaphragm—mediastinal, costal and diaphragmatic pleura—is in close approximation with the other portion of the pleural sac that lines the lung surface—the pulmonary pleura. The narrow space, separating the two pleural leaves, is filled with a viscid lubricating fluid which establishes cohesion between their serous surfaces, but leaves them free to glide over one another, like moist panes of glass which can be relatively shifted, but not forced apart, unless air is made to

get in between them. Contact between the two surfaces is upheld by the air pressure within the lung which is always close to atmospheric pressure.*

Let us assume now that an incision of the chest wall has been made in the course of an operation, opening a "virgin" pleural cavity, viz., an intact cavity and without adhesions between lung surface and chest wall. At once air is admitted between the two pleural leaves, their cohesion is destroyed, and the air pressure on both sides of the visceral (pulmonary) pleura of the exposed lung is equalized. The elastic force of the lung tissue is thereby made active; the lung contracts to a mass of the size of a fist at its hylum—same as in the dog—and the opened side of the thorax is transformed into a cavity. Immediately the respiratory act becomes violently disordered. The excursions of the thorax leave the retracted lung unaffected, because there is no more contact between it and the chest wall; its lobes have lost their function. On the closed side of the thorax, on the contrary, the cohesion between parietal and visceral pleura, and therefore the function of the lung, has been maintained. However, under the difference of air-pressure on both sides of the mediastinum, when the thorax expands during inspiration, the mediastinal structures plus the collapsed lung and the heart with the large blood vessels, move forward and partly into the uninjured side of the thorax, the lung swinging like a pendulum suspended on the trachea as a rod. Inasmuch as the mediastinal contents are attached by means of the lower portion of the pericardium, also, to the diaphragm, the maximal lateral displacement occurs at about the center of the mediastinum. The whole mass moves in the same direction as the chest wall of the uninjured side, that means over towards the side of the lung which is still functioning, and interferes with its proper distention. The functioning lobes are thus, *during inspiration,* held near their normal expiratory distention, with a correspondingly reduced change of air in them and reduced oxygenation of the blood. In expiration the pendulum swings the other way; the whole mass flops back into the open cavity, a to-and-fro rocking of the heart subjecting the large blood vessels to severe bending strains in alternating directions. The mediastinum is now no longer, as under normal condition, the evenly balanced structure, upon which, and upon the rising diaphragm as a cushion, the collapsing chest walls squeeze the air out of the lung through the narrow glottis. With the mediastinum yielding to the one-sided pressure upon it, the air pressure within the lobes of the uninjured side only gradually rises high enough for escape of the tidal air by way of the glottis. A part of this tidal air rather finds an outlet into the incompressible portion of the

bronchial tree of the lobes of the collapsed lung where it has but atmospheric pressure to overcome, and not the additional obstruction represented by the glottis. Thus the main bronchus of the collapsed lung with its first and second divisions—which, as just stated, have retained their normal size and shape on account of the cartilaginous rings within their walls, same as the trachea—becomes a "re-breathing bag" for the functioning part of the lung. In this way the collapsed lung appears to have an inspiration during expiratory movement of the thorax, the air for it, however, not being furnished from without, but representing a part of the expiratory tidal air of the functioning lung; that means air which should have left the respiratory system by way of the glottis. The volume of the tidal air is thus still further reduced, with progressive vitiation of the shifted air.

At the same time a persistent chronic "hyperemia" invariably develops within the collapsed lung on the injured side. Its presence there was proved by most interesting experiments conducted by Cloëtta of Zurich, Switzerland. This phenomenon has so far, it seems, not received the attention which it deserves. The hyperemia of the collapsed lung on the injured side naturally reduces the quantity of blood in the general system, which, as stated before, is altered in its quality by insufficient aëration.

The described interference with the normal exchange of gases in both sides of the lung causes a gradual accumulation of carbon dioxide in the system. This, in turn, produces a steadily increasing irritation of the centers of respiration and circulation by way of the pneumogastrics. In most instances this "vicious circle" soon becomes established after incision of the thorax. Respiration becomes slower and deeper, the number of heart-beats is reduced, while the systolic volume of blood is increased. Dyspnea in its most characteristic picture develops and persists.

Such, in the human being, is the general course of the dreaded "acute pneumothorax." As stated above, it occurs only in a certain percentage of the patients, coming to operation. But who is able to tell beforehand "which" patient will be subject to its deleterious, or even fatal, sequelæ?

The symptoms of acute pneumothorax can not and do not develop, if we prevent the collapse of the lung; that is to say, if we keep the lung on the open side of the thorax in distention and thereby steady the mediastinum. This can be done by the employment of apparatus embodying the "differential air-pressure" method.

Following upon scattered ingenious attempts at preventing the lung collapse with the help of apparatus, by French surgeons (Quénu, 1895, Tuffier, 1896), and American surgeons (Fell, 1888, Matas, 1898), it was Ferdinand Sauerbruch who, in 1904, by his experiments, his scientific investigations and his constructive genius, placed thoracic surgery on a safe basis. By the publication of his differential Pressure Method" and by his apparatus he gave to the surgical world the means for operating on *all* the organs situated within the thorax, under absence of disturbing physical conditions. He

made it possible for the surgeon to operate within the thorax with the same tranquillity of mind and the same precision as in other cavities and parts of the body. The thoracic cavity thereby was opened safely to the surgeon, safely in the real sense of the word, viz., without forcing the operator into taking chances with his patient's life.

He also showed that, in case of injury to the intra-abdominal parenchymatous organs in the vault of the diaphragm (liver and spleen), work upon them could be safely done by the thoracic route (trans-thoracic laparotomy).

The differential pressure method aims at substituting the effect of apparatus for the normal forces sustaining the lung, which were cut out by the opening of the thorax. The apparatus has to supply a force which is equal to the elastic contraction of the lung tissue. The power used is air-pressure.

A difference in air pressure can be obtained:

1. By rarefying the air over the outer surface of the exposed part of the lung; that is to say, by producing there a pressure which is inferior to the atmospheric pressure within the bronchial tree and alveoli—negative (differential) pressure.

2. By increasing above atmospheric pressure the air-pressure within the entire lung—positive (differential) pressure.

Without exception all the various schemes devised for the neutralizing of the injurious effects of the acute pneumothorax are based on that alternative, first pronounced in so many words by Quénæ of Paris.

Making use of either one or the other of these methods in patients suffering from dyspnea in consequence of an acute pneumothorax, one will see the latter disappear and respiration become normal again. One will also see that the lung on the opened side normally participates in the act of respiration. It is further a fact that differential air-pressure interferes neither with the normal respiration nor with the normal circulation of the blood.*

The tangible, practicable result of Sauerbruch's labors was the negative chamber. Its construction and working, its advantages and defects are known to my hearers.

An amplified type of negative chamber, constructed on the basis of Sauerbruch's principles, I had built in New York in 1908, and I experimented with it until 1910. It was then remodeled and became part of the apparatus of the Thoracic Pavilion of the Lenox Hill Hospital of New York City. It permits of working under negative as well as under positive pressure in the course of one and the same operation. The change from one pressure to the other can be effected instantaneously and without the necessity of reversing the position of the patient, assistants, instruments, ec., as would be required in Sauerbruch's chamber, were the pressure to be changed from negative to positive.

A slight increase in pressure has been found in the pulmonary artery with some stasis in the pulmonary vein, also some decrease in arterial blood pressure, when using positive pressure. However, the alterations are of no importance so long as the differential pressure is not pushed, and this is never indicated. One can, therefore, claim that new risks are not incurred by the patient who submits to the application of differential air pressure during operation.

The rectangular negative chamber at the Lenox Hill Hospital is so far the only one produced in America. Originally built as a portable apparatus, and being a first attempt, it is naturally open to improvement in one or the other respect. A round design has on occasion been discussed, constructed so, that the chamber, like other operating rooms, can be washed out with a hose stream; also additions on basis of the Swedish chamber, in which the mask is used in combination with negative pressure, an improvement, which requires no modification of, but only a removable attachment to our present arrangements, and would insure undisturbed asepsis also in operations on the neck in the course of esophageal resections.

The negative chamber is an enlarged pleural cavity. It takes care with the same certainty and reliability of a bilateral as of an unilateral pneumothorax. It represents the most physiological apparatus in existence for complicated intrathoracic work on weak and reduced patients. It permits of the use of differential pressure under general or regional and local anesthesia. It is a splendid physical apparatus, which will always retain its scientific as well as its practical value.

But the negative chamber is expensive and stationary. Surgeon, assistants, nurses and patient have to go to the apparatus; the apparatus can not be brought to the patient. The same holds good for a number of positive (plus) pressure cabinets, in which the patient's head, that is to say, his bronchial tree, together with the anesthetist—entire or in part—are placed under increased pressure.

Sauerbruch's work made a great sensation in the surgical world and met with wide recognition. It also started many minds devising means by which the same ends might be obtained with less expense. In quick succession followed the mask method Brat-Schmieden, Tiegel, Robinson (1908-1910), Meltzer-Auer's Intratracheal Insufflation (1910), and Connell's pharyngeal insufflation (1912), adapted to thoracic surgery by Branower (1913).

Tiegel worked out his apparatus on the basis of the experimental finding that lack of oxygen is the final cause of death in acute pneumothorax. He proved that 1 mm. pressure from a tank filled with pure oxygen suffices to avoid trouble. His splendid practical apparatus is extensively used in European clinics, and should, particularly for use in emergencies, form an integral part of the equipment of every operating room in our country, too. Tiegel's apparatus can be quickly wheeled to the patients' bedside, a feature of great value in case of trouble in the after-treatment of thoracic operations.

Meltzer-Auer's intratracheal insufflation represents the simplest and most nearly perfect of all positive differential pressure methods. Every one of you knows of its well-deserved triumphant march all over the world, within the last eight years. In two directions the method calls for attention and skill—first, that introduction of the tube into the patient's trachea requires profound general anesthesia; and second, that a person is needed

who has been trained to make the introduction of the tube into the trachea properly and gently, without doing harm to the patient.

Intrapharyngeal insufflation, which was originally introduced by Karl Connell of the Roosevelt Hospital, New York, as a method of anesthesia, and later on adopted to thoracic surgery by W. Branower of New York, with the help of an ingenious portable apparatus, promises to become of greatest value for thoracic operations. By insufflating pure air, or air mixed with oxygen, into the pharynx, a sort of air-storage is formed in that locality, in sufficient volume and under sufficient pressure to prevent the flopping of the mediastinum in unilateral pneumothorax and to maintain proper oxygenation of the blood.

In a rough way, foot-bellows and a plain rubber tube, introduced into the pharynx through the nostrils, can substitute the apparatus in case of emergency.

Thus, we now have at our disposal four useful methods for maintaining differential air pressure, from which we can select according to inclination, opportunity, and the needs of the case in hand, four useful, practical differential pressure methods, which enable us to avoid the occurrence of acute pneumothorax. Many of us use such apparatus in our thoracic operations to good advantage and feel that we do not want to be without them.

On the other hand, there are a number of colleagues of high standing who are unwilling to accept differential air pressure as an underlying principle in thoracic surgery, and claim that they are able to get along nicely without its use.

Opposition certainly is wholesome and to be welcomed. It is necessary for the progress of science. But it must be opposition in the right direction. Of course, we all have to individualize. Why should not a surgeon, if he considers it advisable in a given case, do a thoracic operation without employing differential pressure apparatus? I myself have done it in many cases. However, what I claim to be necessary, and always have had in my own cases, is some kind of differential pressure apparatus close at hand, ready for instant use, should the necessity for its use arise in the course of the operation and the patient's welfare demand it. To my mind the time has passed when any surgeon is justified in saying "differential pressure in thoracic surgery is superfluous." To my mind it is wrong to promulgate such views.

For the sake of the proper evolution of thoracic surgery it is equally wrong, I believe, to want to give to the surgery of the lung a special, an exceptional place in thoracic surgery, as some authors have lately been inclined to advocate. We should not separate the surgery of the lung from that of the esophagus or any other intrathoracic organ, but should consider the whole field within the thorax an entity and look at it from a broad and scientific standpoint. We should not separate thoracic surgery into different categories. We speak only of "abdominal surgery," and there is only one "thoracic surgery."

In this connection I must briefly refer to the teachings that have of late emanated from a number of great European surgeons, who worked at the front during the last four years and recently traveled through our country lecturing on their experiences. Under the correct impression that air pressure difference was necessary for safe operating within the thorax, and having no apparatus at hand, they at first abstained in the war hospitals from active interference in chest wounds. Conservatism was their watchword in these war injuries. But, compelled by many unsatisfactory results, they finally dared go ahead without using differential pressure, and saw excellent results in many instances. With the object in view of removing all kinds of foreign bodies in the lung or pleural sac, they made an intercostal incision, cleaned the pleura, pulled out the lobe of the lung in which often the X-ray had previously located the seat of the foreign body, incised the lung, extracted the missile, stitched up the pulmonary wound, dropped the organ back, and closed the chest wall air-tight by suture. Many of these patients recovered.

But is it correct, on the basis of such satisfactory experiences in war surgery in a traumatized and often inflamed and infiltrated lung, and inflamed or infiltrated mediastinal structures, to assert that the acute pneumothorax is something quite negligible, something not worth taking into consideration? Is it correct, on the basis of experiences gained under unusual conditions, to brush aside the well-matured conviction of a century that the acute pneumothorax rather is a matter not to be trifled with, to ignore the decades of endeavor to find means of overcoming its recognized dangers, and to draw the conclusion that differential pressure is a ballast in thoracic surgery? I personally think that it would be an error to accept such a conclusion. To my mind the operator of today has in times of peace no right to jeopardize and take chances with the patient's life, when science offers him the means of avoiding them. Would the surgeon of today dare omit any of the details of aseptic surgery, because the ingenious Spencer Wells, before the antiseptic and aseptic area, successfully performed a number of ovariotomies by simply washing his hands carefully in plain water before the operation? If a modern surgeon were to do his and lose one of his patients he would be condemned, and justly so.

Let us try for a moment to analyze the experience our colleagues have had at the front. For the sake of science it appears necessary to do so, to try to explain the seeming discrepancy between their experience and that had by surgeons when operating on the thorax at our public hospitals in times of peace. How can we explain the absence of worrying symptoms in many of the thoracotomies, when even five to six hours after the wound had been inflicted, the chest was opened freely by incision without the use of differential pressure apparatus?

The fact has been established in the course of the war that over 50 per cent. of the men with chest wounds died on the battlefield. The surviving cases reached the ambulance or field hospital. In them the heart—usually

young, strong, and not diseased—had withstood the acute pneumothorax and hemothorax, and the lung of the unopened side also had adapted itself to the changed conditions. If operated upon by means of an exploratory incision and without pressure apparatus, often the at first serious and threatening symptoms improved. Why? Simply because, as we all know, the wide open pneumothorax, the *free* access and exit of air, is better borne than the pneumothorax coming from a small penetrating wound, through which air has entrance, but very frequently an obstructed exit. After free incision air alone replaces the blood and air that formerly filled the pleural cavity. The mediastinal tissues are apt to be infiltrated with blood, so that there is little flopping. Besides, the surgeon pulls the lung out of the thorax and treats it as the case may require. The pulling out of the lung into the wound opening ("Mueller's trick") steadies the mediastinum still further. The lung is then attended to, the pleura cleansed, and the thorax closed hermetically by sutures; a temporary artificial pneumothorax is left behind. The latter, as shown by Bastianelli's splendid investigations on the Italian front, favors the healing of the injured lung and its gradual expansion with advancing absorption of air.

The results obtained by our colleagues in military service by means of aggressive surgery in wounds of the lung have certainly been brilliant and deserve the highest praise. But to draw any sweeping conclusions from their experience *with reference to the question of whether or not the employment of differential air pressure in thoracic surgery in general is a necessity* would, to my mind, be a serious mistake. How many of the wounded, who died after thoracic operations, might have recovered, could some differential pressure method have been employed during the surgeon's work, can, of course, not be estimated.

The simplicity of the above-described operative procedure in war injuries of the thorax may perhaps have impressed particularly those who never before had intentionally entered the thorax in civil practice, and who now under war conditions were, by sheer necessity, driven to thoracic operations. Under the stress and strain of their work and their often unexpected brilliant results of radical interference, it can be understood that many were carried away by their enthusiasm, that they generalized and gained the impression that employment of differential air pressure in thoracic surgery is superfluous. But they forgot that traumatic chest surgery is only *one small chapter* of thoracic surgery.

This, "whether or not" to use differential air pressure in thoracic operations is, it seems to me, the most vital question of the hour for the further safe and rapid evolution of thoracic surgery.

The idea that differential pressure apparatus are superfluous, at least in lung surgery, has naturally also got into the medical press, and thereby been widely disseminated. What wonder that our colleagues are bewildered and do not know which opinion to accept! But a few weeks ago I met a colleague at the Academy of Medicine in New York, who works at a hospital

with plenty of accidental chest injuries. We got into a discussion on thoracic surgery and differential air pressure. He said: "Doctor, nobody knows at the present moment where he stands. If you and your friends of the American Association for Thoracic Surgery want to do the profession a favor, throw some light on this vital question and state whether you think the hospitals ought to provide means for operating within the thorax or not."

Most earnestly would I invite the colleagues who believe that thoracic surgery *in general* can well get along without provision for the maintenance of the physiologic difference in air pressure existing in the chest, to come into the arena for an open discussion of this vital question which has been agitating many minds for the last twenty-five years, particularly for the last fifteen years, and submit their experiences and case histories. Let us discuss this vital question fully, but let us settle it, at least among ourselves.

On the basis of practical experiences in this one chapter of traumatic chest surgery, gathered during the war, modern thoracic surgery in general —I beg to emphasize this once more—can not afford to throw overboard what it has slowly built up within the last fifteen years, modern thoracic surgery in general can not afford to loosen the safe foundation on which it rests, namely, the recognition of the absolutely vital necessity of having ready for use a differential air pressure apparatus whenever a free pleural cavity is invaded, whenever a "virgin" non-adherent pleura has to be traversed in order to reach affected organs lying beyond it within the thoracic cavity.

In the early part of November of last year I had the privilege of discussing all these important questions with the five members of the commission that had come over from England, France and Italy to attend the American Congress of Surgeons. All five came to the Thoracic Pavilion of the Lenox Hill Hospital. They examined the differential pressure apparatus there on hand: the negative chamber and the positive cabinet, Tiegel's mask apparatus, and the apparatus for insufflation. After a prolonged talk, three of the five took my point of view and conceded the necessity of doing thoracic operations with proper preparedness for differential pressure, negative or positive.

And let it be remembered that mask method and insufflation method, intratracheal as well as intrapharyngeal, all work on the principle of positive (plus) pressure within the bronchial tree; that is, on the principle of differential air pressure.

Gentlemen, I would ask you, not to consider the foregoing remarks a reflection upon what other colleagues have said and done, but to take them for an honest attempt, based on personal experience and conviction, to assist in finding the truth, and to help in accelerating the evolution of thoracic surgery for the benefit of suffering mankind.

After all, the safeguarding of the life of the patient entrusted to his care is the first duty of the surgeon.

BLOOD FORMATION IN THE LIVER AND SPLEEN IN EXPERIMENTAL ANÆMIA.[1]

Roger S. Morris, M. D.

Cincinnati.

(From the Laboratory of the Second Medical Clinic in Munich,[2] Professor Fr. Müller, Director.)

It is a well-established fact that the chief function of the bone marrow in adult life is hæmatopoiesis. In embryonic life the liver and spleen are hæmatopoietic organs, but in extrauterine life the marrow unaided seems to be adequate for the formation of the blood and this function is then lost by the liver and spleen, which differ in a corresponding way histologically at these two stages of life. Shortly after birth there is apparently less need for rapid production of blood corpuscles than in the embryo, and this results, therefore, in the absence of recognizable hæmatopoietic (myeloid) tissues in liver and spleen, while at the same time evidence of extensive proliferation is less marked in the bone marrow. If, however, unusual demands are made upon the bone marrow for one reason or another, as, for example, through the loss of a large quantity of blood from hæmorhage, signs of increased activity are found; and in certain instances, as in most cases of pernicious anæmia, the alteration of the marrow may be such that it resembles in a remarkable manner that seen in the embryo—a reversion of the marrow to the embryonic type, as Ehrlich pointed out many years ago. Here, to all intents and purposes, the problem of the pathological physiology of blood formation in severe anæmias has remained until the recent publications by Meyer and Heineke (1, 2) of the results of their studies, which prove, they believe, a similar reversion to the embryonic type on the part of the liver and spleen in cases of grave anæmia.

In a careful examination, both clinical and histological, of eleven cases of severe anæmia (1) which came to autopsy (seven cases of pernicious anæmia, two of anæmia following sepsis, one of anæmia associated with cardiac disease, and one of so-called leukanæmia) and, in their second more complete study (2), of an additional two cases of pernicious anæmia diagnosed at autopsy, Meyer and Heineke have found strong evidence of blood formation in the liver and spleen. The organs were studied from smears made from the freshly cut surfaces post-mortem and from histological sections. In the spleen they found alterations in all instances; these consisted in decrease in size of the follicles and collections of mononuclear cells, varying greatly in size and in the relation of nucleus to cell body, within the venous sinuses—the so-called Billroth's veins of the spleen. These cells they identified from a study of the smears and sections, as normoblasts, myelocytes, and mononuclear, non-granular, "lymphocyte-like" cells. Changes in the liver were not so constantly present, but were found in seven cases.

They were of two kinds: (a) In three instances they found groups of mono-
nuclear cells collected in the liver capillaries, chiefly in the peripheral portion
of the lobules, consisting of lymphocyte-like cells, normoblasts, and mye-
locytes, and (b) in four cases there were collections of large mononuclear
cells rich in protoplasm in the periportal connective tissue, usually arranged
about the cells, with many mononuclear eosinophile cells also. In the smears
made from both spleen and liver the proportion of nucleated red blood cells
and myelocytes greatly exceeded that found in preparations made from the
blood. The liver sections corresponded very closely in appearance with
those of the human embryo's liver at about the seventh month, while the
spleen was also embryonic in type. No collections of cells like those described
in the liver and spleen were found in any other organs, and the authors felt
justified in the belief that the changes represented true blood formation
rather than a wandering in of cells from the circulation, the cell-nests re-
sembling closely those seen in the bone marrow.

With the view of determining whether similar changes could be repro-
duced in animals by the administration of substances known to cause anæmia,
experiments were begun by the writer at the suggestion of Prof. Müller and
Dr. Meyer. The rabbit was the animal chosen and pyrodin (acetylphenyl-
hydrazin) was selected as the toxic agent. The attempt was made to pro-
duce a chronic anæmia of rather severe grade, so that the bone marrow
would be overtaxed in blood formation. By this means it was hoped that
the liver and spleen would reassume one of their embryonic functions and
assist in the production of blood.

The animals were kept in well-cleaned and ventilated cages and were
fed with oats and greens daily. Frequent examinations of the blood were
made, including counts of both red and white cells, estimation of hæmo-
globin, and smears. Pyroden was given about 5:00 p. m., the dose depend-
ing upon the blood count made earlier in the afternoon. A solution of
pyrodin in water was prepared in which 1 c.c. equaled 0.005 gram pyrodin.

Experiment A: Rabbit I. Male. Weight, 2,665 grams. Pyrodin ad-
ministered by stomach tube.

Date 1905	R. B. C.	W. B. C.	Hb.		Pyrodin	Remarks
30-VI	5,550,000	12,000				
3-VII	5,200,000	7,080			0.015	
4-VII					0.01	
5-VII	5,350,000	9,600	60%	(Sahli)	0.02	
6-VII	4,090,000				0.02	
7-VII	3,650,000	14,732	43%	"	0.03	
8-VII	2,875,000				0.02	
10-VII	2,105,000	17,166	25%	"	0.02	No free Hb. in serum.
11-VII	2,200,000				0.02	
12-VII	2,155,000	11,776	17%	"	0.02	
13-VII	1,830,000				none	Animal weak. Wt. = 1,964 gms.
14-VII	1,940,000	13,954	25%	"	none	
15-VII	2,375,000	11,354	31%	"	"	
15-VII	2,375,000	11,354	31%	"	0.02	
17-VII	2,435,000	5,820	46%	"	0.03	Fresh solution of pyrodin.
18-VII	3,490,000	5,154	46%	"	0.035	Serum clear.
19-VII	3,125,000					

Date 1905	R. B. C.	W. B. C.	Hb.	Pyrodin	Remarks
20-VII	2,635,000	8,660	37% (Sahli)	0.03	
21-VII	2,265,000			0.03	Serum faintly pink.
22-VII	1,910,000	15,466	26%	"	0.03	Abscess of left ear.
24-VII	1,080,000	18,688	25%	"	none	
25-VII	1,930,000			0.03	
26-VII	1,937,000	9,622	34%	"	0.03	
27-VII	2,245,000			0.04	
28-VII	1,785,000	12,622	31%	"	0.03	Fresh solution of pyrodin.
29-VII				0.02	
30-VII	1,875,000	11,266	29%	"	0.03	
31-VII	1,230,000			0.02	
1-VIII	1,450,000	33,822	23%	"	0.025	Ear abscess evacuated.
2-VIII	1,925,000			0.03	
3-VIII	1,565,000	8,600	23%	"	0.03	
4-VIII	1,385,000				Died.

Death occurred some time between 11:45 a. m. and 2:45 p. m. At autopsy the body was warm. There was slight rigor mortis in the legs. Weight = 2,065 grams. All of the organs were very dark in color. The spleen was enlarged, measuring 8 x 1.5 x 2 cm. The bone marrow was dark reddish brown in both femurs. The lungs were air-containing throughout and there were numerous pin-head hæmorhages on the surfaces. The kidneys showed pigmentation of the cortex; this was especially marked along the inner edge. Heart muscle was paler than normal. There was very little blood in the organs. No fluid in peritoneum, pleuræ or pericardium.

MICROSCOPICAL EXAMINATION.—The tissues, fixed in alcohol, mercuric chloride and acetic acid, and formaldehyde, were embedded in paraffin and in celloidin, sectioned, and stained with hæmatoxylin and eosin, van Gieson's stain, and borax carmine with potassium ferrocyanide and hydrochloric acid.

Bone Marrow.—The marrow of the shaft of the femur, normally fatty in full-grown rabbits, showed marked hyperplasia, the fatty marrow being entirely replaced by myeloid tissue. A study of smears, stained with hæmatoxylin and eosin, May-Grünwald's stain, and Ehrlich's triple stain, in conjunction with that of the sections, shows that the non-granular mononuclear cells (myeloblasts) are greatly in the majority. There are many normoblasts and many intermediates, but no typical megaloblasts. Myelocytes are also numerous. There are a few phagocytes and many megalokaryocytes (see Fig. 1).

Spleen.—There is marked destruction of the cells of the pulp. The follicles are diminished in size and in some instances the central artery is almost completely devoid of lymphoid tissue. *In the venous sinuses* there are large *nests of mononuclear cells* with non-granular protoplasm and rather deeply staining nuclei (see Fig. 2). There is an enormous number of phagocytes containing fragments of red blood cells and brown amorphous pigment, both in the capillaries and venous sinuses and in the pulp. Megalokaryocytes are fairly numerous. *Smears* made from the freshly cut surface of the spleen show many non-granular mononuclead cells like those in the bone marrow, varying in size from that of a red blood cell to a cell whose diameter is twice as large or greater, the protoplasm being very basophilic, the nucleus a little paler (May-Grünwald stain). Many of the nuclei have brick red blotches

which extend at times into the protoplasm. From the former cell one sees apparently all gradations to the typical myelocyte, i. e., from cells having few pseudo-eosinophile or eosinophile granules to those having many. There is a moderately large number of myelocytes. In the smears there are also a few normoblasts. Very few polymorphonuclear pseudoeosinophiles are seen and rarely one finds a mastcell. There are many pale, free nuclei. Phagocytes are present.

Liver.—The section of the liver presents a remarkable picture. The liver cells are well preserved, but show considerable pigmentation, hæmosiderin being present in large amount. The *liver capillaries* are much *widened, and in them, especially in the periphery of the lobules* (see Fig. 3), are *nests of mononuclear cells* (Fig. 4), having non-granular protoplasm and deeply staining nuclei (hæmatoxylin and eosin). The cells of the intra-capillary nests resemble large lymphocytes, though at times apparent erythroblasts (normoblasts) and undoubted pseudoeosinophile myelocytes are seen. Some of the cells show mitotic figures. The number of cells seen in the central veins of the lobules and in the larger vessels of the liver is relatively much less than that in the capillaries of the peripheral part of the lobules, while in the central zone of the lobules nucleated cells are very scarce in the capillaries. Occasionally a *megalokaryocyte* is found, often in connection with a collection of mononuclear cells (see Fig. 5), at times independent of a cell-nest. In the capillaries there are also phagocytes like those seen in the spleen. No collections of mononuclear cells are found in Glisson's capsule, though there is a myelocyte occasionally. *Smears* made from the liver resemble in every way those made from the spleen.

Kidneys.—These organs show no noteworthy alteration except for marked hæmosiderosis of the cortex.

Lungs.—There is moderate congestion. A few megalokaryocytic emboli are seen.

The remaining organs showed nothing of importance.

In this experiment we have, then, a chronic anæmia produced by administration of pyrodin in which a maximal effort has been made on the part of the organism to regenerate the blood. Not only is the bone marrow hyperplastic, but the liver and spleen which present a very striking resemblance to those organs in the rabbit's embryo during the stage when they are actively engaged in blood formation, may be assumed to aid in the formation of blood. The picture parallels that described by Meyer and Heineke in pernicious anæmia in man to a striking degree in the presence of myeloid tissue in both liver and spleen, and further resemblances to pernicious anæmia are found in the high color index which existed during life, the blood crises, the presence of "nuclear particles" in the red blood cells (to be described in another paper), the myeloblastic type of bone marrow, the phagocytosis in the hæmatopoietic organs, and the hæmosiderosis of liver, spleen, and kidneys.

Experiment B: Rabbit II. Male. Weight, 1,285 grams. Pyrodin given subcutaneously and by stomach tube.

Date 1905	R. B. C.	W. B. C.	Hb.	Pyrodin	Remarks
1-VII	5,200,000	9,000			
3-VII				Gm. 0.01	
4-VII	3,055,000	7,140	40%	(Sahli) 0.005	
5-VII				0.005	
6-VII	2,700,000	9,732	32%	" 0.005	
7-VII	2,900,000			0.01	
8-VII	2,675,000	14,600	35%	" 0.01	
10-VII	2,350,000			0.01	
11-VII	2,655,000	16,110	41%	" 0.01	Hb. estimation verified.
12-VII	2,265,000			0.01	
13-VII	2,465,000	8,510	35%	" 0.015	Wt. 1,335 gms.
14-VII	2,180,000	10,688		0.01	
15-VII	2,330,000	5,576	37%	" 0.015	
17-VII	2,410,000	11,600	36%	" 0.02	
18-VII	2,610,000			0.025	Fresh solution of pyrodin
19-VII	2,585,000	10,884	38%	" 0.03	
20-VII	2,160,000			0.02	
21-VII	2,060,000	25,532	32%	" 0.025	
22-VII	1,725,000			0.02	
23-VII	1,212,000	33,488	26%	" none	
24-VII	1,835,000			0.02	
25-VII	2,085,000	10,510	35%	" 0.03	
26-VII	1,262,000			0.02	
27-VII	950,000	16,510	21%	" none	
28-VII	1,775,000			0.025	
29-VII	1,950,000	26,310	34%	" 0.03	
30-VII	1,850,000			0.03	
31-VII	1,720,000	19,800	22%	" 0.03	
1-VIII	1,480,000			0.035	
2-VIII	1,365,000	21,044	22%	" 0.03	
3-VIII	1,500,000			0.03	
4-VIII	1,375,000	25,954	25%	" none	
5-VIII	1,475,000			0.03	Pyrodin by stomach tube.
7-VIII	2,100,000	14,354	38%	" 0.03	Pyrodin by stomach tube.
8-VIII	2,230,000			0.04	Pyrodin by stomach tube.
9-VIII	2,125,000	30,250	25%	" 0.04	Fresh solution of pyrodin.
10-VIII	1,415,000			0.04	Pyrodin by stomach tube.

Death during the night. Autopsy at 12:15 p. m. There was a small amount of clear, light yellow fluid in the peritoneum. Right lung showed moderate hypostasis and œdema. Otherwise the organs resembled in every particular those from rabbit I.

MICROSCOPICAL EXAMINATION.—The tissues from this rabbit, as well as those from the remaining animals, were all treated as in rabbit I, experiment A.

Bone Marrow.—This resembles in all respects that seen in rabbit I. In the smears, however, there are a few nucleated red cells which may be classed as megaloblasts.

Spleen.—There is marked necrosis of the pulp and the Malpighian follicles are reduced in size. In places in the venous sinuses there are groups of mononuclear, non-granular cells like those in experiment A. In one group there were two megalokaryocytes and several phagocytes, and in one of the non-granular cells a mitotic figure was seen. Hæmosiderosis is marked. The erythrocytes throughout the spleen are for the most part

shrunken and distorted. *Smears*, stained as in experiment A, show very many cells resembling lymphocytes with a moderate number of normoblasts and myelocytes which, however, seem less numerous than in rabbit I. There are many phagocytes and practically every red blood cell is distorted.

Liver.—There is marked fatty degeneration, affecting chiefly the cells of the central part of the lobule. There is no dilatation of the capillaries and no intracapillary nests of cells are to be seen. No megalokaryocytes are found. There is considerable hæmosiderosis. *Smears* show a few polymorphonuclear pseudoeosinophiles. Very rarely one finds a normoblast or a myelocyte; they seem to be about as numerous as they are in the heart's blood. Mastzellen are comparatively numerous. A few phagocytes are seen.

Kidneys.—Marked hæmosiderosis of the cortex; otherwise practically negative.

The remaining organs are negative.

The spleen, which has been active in this experiment as a hæmatopoietic organ, has assisted the bone marrow in the attempt to compensate for the anæmia, but there is no evidence of hæmatopoiesis in the liver.

Experiment C: Rabbit III. Male. Weight, 2,170 grams. Pyrodin given by stomach tube.

Date 1906	R. B. C.	W. B. C	Hb.	Pyrodin	Remarks
11-IV	5,050,000	9,020	53%	(Miescher)	none
18-IV	6,025,000	12,400	62%	"	0.01
19-IV	5,820,000				0.02
23-IV	3,850,000	12,500	44%	"	0.02	Rabbit seems lifeless.
23-IV	3,487,000				0.025
25-IV	3,275,000	14,160	34%	"	0.04
26-IV	2,125,000				none
27-IV	1,843,000				"
28-IV	1,093,000	12,480	23%	"	"
30-IV	1,925,000	7,000	39%	"	"
1-V	3,441,000	8,600	47%	"	0.03
2-V	2,075,000	10,640	39%	"	none
3-V	3,721,000	9,280	51%	"	"	Difficulty in passing tube.
4-V	3,833,000	5,600	51%	"	"	Difficulty in passing tube.
5-V	4,087,000	6,932	58%	"	0.035
7-V	2,975,000	12,532	42%	"	"
8-V	2,750,000	13,120	33%	"	0.035
9-V	2,660,000	15,600	32%	"	0.035
10-V	2,450,000	26,800	25%	"	0.04
11-V	1,500,000	26,300	17%	"	none
12-V	1,400,000	20,400	19%	"	0.025
14-V	2,312,000	5,849	28%	"	0.04
15-V	2,300,000	6,620	26%	"	0.04	Fresh solution of pyrodin.
16-V	1,993,000	19,520	23%	"	0.04
17-V	1,858,000	8,700	15%	"	none
18-V	1,730,000	7,464	16%	"	"
19-V	1,935,000	3,776	21%	"	0.04
21-V	2,566,000	4,088	28%	"	0.045
22-V	2,020,000	7,064	20%	"	none
23-V	2,012,000	17,600	22%	"	0.04
24-V	1,762,000	5,552	18%	"	none
25-V	1,525,000	8,900	17%	"	"
26-V	1,735,000	7,464	16%	"	"
28-V	2,225,000	3,700	28%	"	0.045

Date 1906	R. B. C.	W. B. C.	Hb.	Pyrodin	Remarks
29-V	2,360,000	5,200	19% (Miescher)	0.045	
30-V	1,880,000	16,800	15%	"	0.045
31-V	1,293,000	21,500	12%	"	"
1-VI	1,044,000	18,932	11%	"	"
2-VI	1,341,000	10,044	11%	"	"

Death occurred between 10:00 and 11:00 a. m. on June 4, 1906. Autopsy at 3:00 p. m.

There were small yellowish nodules in the liver, some of which had ex tended to the surface of the organ; they were slightly elevated, flat across the top, and rather firm in consistency. No areas of softening were found in them on section. In other respects the organs differed, macroscopically, in no essentials from those in the preceding rabbits.

MICROSCOPICAL EXAMINATION.—*Bone Marrow.*—There is marked hyperplasia of the myeloid tissue, the granular marrow cells (myelocytes) being in the majority. The islands or cell-nests described by Bunting are well seen and many of the large non-granular cells in the center of the nests show karyokinetic figures. Phagocytes are present. In the *smears* there are many free pseudoeosinophilic granules; there are very few intact myelocytes.

Spleen.—This resembles the spleen in rabbits I and II in the decrease in size of the splenic follicles, the diminished number of cells in the pulp, and the presence of a few megalokaryocytes. Phagocytes are present in enormous numbers. A few pseudoeosinophile myelocytes are found in the pulp. In the venous sinuses and rarely in a capillary, collections of mononuclear cells resembling large lymphocytes are seen; at times a megalokaryocyte is present in these collections of mononuclear cells. Evidences of mitosis are not lacking in the cells collected in the venous sinuses. *Smears* show large numbers of nucleated reds, as many as six being found in one field (Leitz, 1/12 oil immersion; ocular, IV). The majority of the nucleated reds are normoblasts, though there are many intermediates and rarely a megaloblast ?). No definite cell division figures are found in the smears. There is a great number of lymphocyte-like cells resembling the non-granular, mononuclear cells of the bone marrow. A moderate number of pseudoeosinophile myelocytes is present. Mastzellen are very scarce.

Liver.—The liver cells show little change other than a moderate pigmentation of the cells of the peripheral zone of the lobules. In the liver capillaries, both in the central and peripheral zones, there are many pseudoeosinophile leucocytes, mostly polymorphonuclear with only an occasional mononuclear. Megalokaryocytes are not seen. Glisson's capsule is un altered. The nodules found at autopsy present a central necrotic area surrounded by granulation tissue. *Smears* show many polymorphonuclear pseudoeosinophiles, very few normoblasts and mastzellen, few pseudoeosinophile myelocytes.

The remaining organs are negative except for pigmentation of the renal cortex.

Experiment D: Rabbit IV. Male. Weight, 2,360 grams. Pyrodin given subcutaneously.

Date 1906	R. B. C.	W. B. C.	Hb.	Pyrodin	Remarks
12-IV	5,855,000	4,176	55%	(Miescher)	none
18-IV	5,662,000		59%	"	0.01
19-IV	5,860,000	6,800	59%	"	0.015
23-IV	5,612,000		51%	"	0.015
24-IV	4,820,000	5,200	44%	"	0.03
25-IV	5,170,000				0.04
26-IV	3,125,000	8,844	43%	"	0.03
27-IV	1,664,000				none
28-IV	1,406,000	6,920	11%	"	"
30-IV	1,440,000	2,800	17%	"	"
1-V	1,941,000	2,664	26%	"	"
2-V	3,360,000	2,488	39%	"	0.03
3-V	3,164,000	3,100	45%	"	0.035
4-V	2,714,000	4,700	43%	"	0.03
5-V	2,400,000	6,400	43%	"	0.03
7-V	2,100,000	7,128	35%	"	0.03
8-V	2,125,000	13,800	25%	"	0.035
9-V	1,662,000	18,080	15%	"	none
10-V	1,237,000	4,932	18%	"	"
11-V	1,807,000	5,376	24%	"	0.025
12-V	2,014,000	3,864	28%	"	0.035
14-V	1,468,000	4,480	22%	"	0.03
15-V	1,785,000	4,852	20%	"	0.035
16-V	1,262,000	11,200	15%	"	none
17-V	1,750,000	4,932	19%	"	"
18-V	2,160,000	2,640	24%	"	0.035
19-V	2,050,000	3,100	23%	"	0.035
21-V	1,281,000	3,360	12%	"	none Animal weak. Fur rough.

Animal died between 11:00 a. m. and 1:00 p. m. on May 22, 1906. Autopsy at 5:00 p. m. Large red clots in both ventricles and extending into the aorta; practically no fluid blood in any of the vessels or organs. The latter are macroscopically the same as in rabbit I. As in the preceding animals, no lymph glands or hæmolymph glands were found.

MICROSCOPICAL EXAMINATION.—*Bone Marrow.*—The section shows marked hyperplasia of the bone marrow of the myeloblastic type. In the *smears* the myeloblasts are by far the most numerous, the erythroblasts and granular marrow cells being relatively few in number.

Spleen.—The alterations in the spleen resemble those seen in the three previous experiments, but they are less marked. Megalokaryocytes are present. *Smears* show, in addition to many lymphocyte-like cells, a few normoblasts and myelocytes.

Liver.—Sections show very little alteration. In the *smear* only two normoblasts were found after prolonged search, not more than smears from the blood showed, it seemed.

Kidneys.—Marked pigmentation of the convoluted tubules is found.

Lungs.—There is marked œdema and moderate congestion. In the capillaries one finds a few megalokaryocytes.

Experiment E: Rabbit V. Female. Weight, 1,900 grams. Pyrodin given by stomach tube.

Date 1906	R. B. C.	W. B. C.	Hb.	Pyrodin	Remarks
16-X	5,500,000	8,200	61%	(Miescher)	0.01	
17-X	5,500,000	8,240	62%	"	0.02	
18-X	4,330,000	9,760	57%	"	0.02	
19-X	4,310,000	6,240	48%	"	0.035	
20-X	3,425,000				none	
22-X	2,055,000				"	
23-X	1,840,000	9,280	29%	"	"	
24-X	2,105,000	7,200	39%	"	"	
25-X	2,415,000	5,680	39%	"	0.025	
26-X	2,880,000	7,760	40%	"	0.035	
27-X	2,990,000	6,000	43%	"	0.045	
29-X	2,410,000	7,360	34%	"	0.045	
31-X	2,265,000	6,320	31%	"	0.04	
1-XI	2,735,000	5,680	38%	"	0.05	
2-XI	2,600,000	3,680	29%	"	0.03	Fresh solution of pyrodin.
3-XI	2,510,000	6,160	26%	"	0.04	
5-XI	2,585,000	17,840	29%	"	0.04	
6-XI	2,310,000	5,600	30%	"	0.04	
7-XI	2,660,000	5,520	35%	"	0.045	
8-XI	1,850,000	9,000	25%	"	none	
9-XI	2,070,000	6,640	30%	"	0.04	
10-XI	2,150,000	5,280	30%	"	0.045	
12-XI	2,275,000	7,040	30%	"	0.05	
13-XI	2,090,000	4,720	26%	"	none	
14-XI	2,730,000	8,720	34%	"	0.07	
15-XI	2,775,000	5,760	31%	"	0.14	

Rabbit was found dead at 8:00 a.m. Autopsy at 11:00 a.m. Rigor mortis present. Spleen 8.5 x 1.5 x 0.5 cm. Right lobe of liver greatly atrophied. Two small nodules in liver and the normal mottling of the organ lost. Very small amount of slightly reddish ascitic fluid. Otherwise the findings at section were the same as in rabbit I.

MICROSCOPICAL EXAMINATION.—*Bone Marrow.*—Both sections and smears show myeloblastic hyperplasia of the bone marrow.

Spleen.—The section resembles closely that from rabbit IV. A few pseudoeosinophile myelocytes are seen in the meshes of the pulp and there are a few megalokaryocytes. There are small nests of mononuclear, non-granular cells, which look like lymphocytes, in the venous sinuses. *Smears* of the spleen show many lymphocyte-like cells, rarely a nucleated red blood cell, and a few myelocytes.

Liver.—There is some cloudy swelling and pigmentation of the liver cells. No nests of cells are to be seen in the capillaries. The smears are negative.

Lungs show moderate œdema. There are no megalokaryocytes in the capillaries.

The other organs, excepting the kidneys which present the usual changes, are negative.

Experiment F: Rabbit VI. Female. Weight (?)—average size. Pyrodin given by stomach tube.

Date 1906	R. B. C.	W. B. C.	Hb.	Pyrodin	Remarks
16-X	4,090,000	8,080	61% (Miescher)	0.01	
17-X	4,705,000	11,640	60%	"	0.02
18-X	4,025,000	8,640	52%	"	0.02
19-X	4,260,000	10,000	52%	"	0.035
20-X	3,590,000				Animal weak.
22-X	1,535,000			none	

At about 10:00 a. m. on October 23, 1906, rabbit died. Autopsy at 3:30 p. m. The organs were all negative except for marked anæmia. There was very little fluid blood. No bleeding on section of liver. Clotted blood in heart, arteries, and veins. Bone marrow grayish brown. Spleen, 5 cm. long.

MICROSCOPICAL EXAMINATION.—*Bone Marrow.*—The fatty marrow of the femur is largely replaced by cellular myeloid tissue in which there are a few normoblasts and a few myelocytes, the majority of the cells being nongranular mononuclears (myeloblasts). There are many megalokaryocytes and a few phagocytes. *Smears* reveal nothing additional.

Spleen.—The pulp is poor in cells. The capillaries and venous sinuses are greatly widened and filled with blood. The follicles are slightly diminished in size. There is a moderate number of phagocytes. A few very small collections of mononuclear, non-granular cells are found in the venous sinuses. In the *smears* many cells resembling the myeloblasts of the marrow are present; there are very few myelocytes and no normoblasts seen.

Liver.—There is nothing unusual with the exception of a few giant cells in the liver capillaries. Smears show very few non-granular mononuclear cells like those seen in the spleen; no normoblasts or myelocytes are found.

Kidneys.—Slight cloudy swelling and pigmentation of the cortex.

Lungs.—An occasional megalokaryocytic embolus is to be seen.

No cause can be found for the rapidly progressive pernicious course of the anæmia in this case. The rabbit received exactly the same doses of pyrodin (and on the same days and hours) as rabbit V; in the one the blood count gradually fell till exitus lethalis occurred less than nine days after the beginning of the intoxication; in the other the fall in the number of the erythocytes was less pronounced and a fatal issue did not result. The probable explanation would seem to be, in part at least, defective powers of hæmatogenesis in rabbit VI, such as one sees in the so-called aplastic pernicious anæmia in man. This assumption is further supported by the practical absence of nucleated red blood cells from the circulating blood during the entire course of the anæmia. In this case there was not, however, aplasia of the blood forming organs. It is true that there was not complete myeloid transformation of the fatty marrow of the femur, and evidence of hæmatopoiesis in the spleen, if present, was slight, but it is uncertain whether the hyperplasia of the blood forming organs in this instance is any less than that which might be found in the rabbit ordinarily after an acute anæmia

lasting a little more than eight days. No alterations, other than those characteristic of pyrodin poisoning, were found in any of the organs, and there is, therefore, a similarity between the result obtained in this experiment and certain cases of "aplastic" anæmia in man, for in the latter the disease process results, it seems probable, from excessive blood destruction with little or no evidence of compensatory blood formation.

The earliest attempt at studying hæmatopoiesis in anæmia of adult animals experimentally was made by Bizzozero and Salvioli (3) in 1881. After venesection in guinea-pigs and dogs they found large numbers of nucleated red blood cells in the spleen, which normally contains few, as well as in the bone marrow. In rabbits, whose spleen contains no nucleated reds normally in adult life, they were unable to produce changes similar to those obtained in guinea pigs and dogs. They believed, as a result of their experiments, that the spleen was active in regenerating the blood. Later Gibson (4) repeated their experiments on dogs in part, with the same result, and he made the observation that many of the nucleated reds in the spleen presented division figures in the nuclei, a point strongly in favor of their local origin. In 1890, there appeared the work of Howell (5), in which he was able to show that, after severe and repeated bleedings, and in some instances after a single strong hœmorrhage, nucleated red blood corpuscles were demonstrable in the spleen of the cat with every indication that they were multiplying there, though normally these cells are not found in the cat's spleen in postnatal life.

In studying the spinal cord changes occurring in experimental anæmia of rabbits produced by pyrodin, von Voss (6) noted that there was a deposition of granular pigment in the spleen with areas of necrosis, fatty degeneration in the liver, and in the kidneys all stages of parenchymatous nephritis. Tallquist (7) directed his attention especially to the iron content of the organs of dogs, in which both acute and chronic anæmia had been produced by the administration of pyrodin and of pyrogallol, and was able to prove in many instances a marked increase in the iron of the liver with considerable deposition of hæmosiderin in the spleen, kidneys, and bone marrow frequently. In my own experiments there was a marked reaction for hæmosiderin in liver, spleen, and kidneys in rabbits I and II, the only ones in which it was tried, but the equally marked pigmentation of the cells in the remaining animals makes it probable that the same holds true in all six. In the bone marrow in my experiments the pigment is contained chiefly in phagocytes. In only one instance was fatty degeneration of the liver found, as von Voss reported, while in none of my animals were the renal changes sufficiently marked to consider the existence of a nephritis. Very recently Rothmann and Mosse (8) have studied the effect of chronic pyrodin poisoning in dogs and give additional results of the general findings at autopsy (Mosse). No changes were found in the lymph glands. The spleen, enlarged at autopsy as in the reports of all previous workers, contained much pigment and the follicles were entirely pro-

served. The characteristic pulp cells were not well preserved. The kidneys showed the usual changes, they say, in the epithelial cells of the straight and convoluted tubules. Hæmosiderosis of the liver was noted. Most interesting was the condition of the hyperplastic bone marrow, similar to that described by Reckzeh (9) in dogs after pyrogallolanæmia. The cells often designated "Stammzellen" or myeloblasts were present in very large numbers, there were many normoblasts and few granular cells. Unlike others, Reckzeh described megaloblasts in addition to normoblasts in the bone marrow. The marrow of the femur in my experiments showed myeloblastic hyperplasia in all instances with the exception of rabbit III, in which there was a chronic infection, a fact which may explain the large numbers of granular cells.

Lastly, and of greatest interest in connection with the present work, Bunting (10) in 1906 showed, among other things, that chronic anæmia of rabbits, produced by the administration of saponin, lead in some instances to collections of cells in the venous sinuses of the spleen, just as Meyer and Heineke had found in man and as I found in my first two experiments.³ "The peripheral venous sinuses of the spleen were much dilated and crowded with cells of the marrow type chiefly of the erythrogenetic series, but including many megalokaryocytes and leucocytes. The nucleated red blood cells were grouped much as in the marrow and showed numerous mitotic figures. The veins of other organs are practically free from nucleated red cells, except for an occasional small group in the liver and the constant presence of megalokaryocytic nuclei in the capillaries of the lung." In Bunting's rabbits the anæmia did not become very severe, and this he attributed to the vacarious blood formation occurring in the spleen. It seems much more likely, however, that in some way tolerance to the poison was established, for in my first experiment, where evidence exists of hæmatopoiesis in bone marrow, spleen, and liver as well, there developed, nevertheless, a profound anæmia with fatal issue. As in his animals, I have found megalokaryoytes in the capillaries of the lungs, but not constantly. They were not present in the liver capillaries in Bunting's experiments.

The anæmia produced by pyrodin is due, not to any interference with normal blood formation, so far as is known, but to a great increase in blood destruction. Pyrodin acts upon the red blood cells causing shrinkage and deformity, and as Heinz (11) has demonstrated, these effects are most pronounced about twenty-four hours after the administration of the drug. In my experimental animals the color index remained high, as in Tallquist's experiments. Fortunately in the present work, the complete blood examination was made always between twenty-two and twenty-four hours after the administration of the pyrodin. The changes in the red blood cells will be discussed in another paper. Suffice it for present purposes to say that the deformities in the red blood corpuscles which Heinz described occurred in all of my rabbits. The serum was examined several times for the presence of

³ Mentioned in the preliminary report of Meyer and Heineke, 1905 q. v.

free hæmoglobin, but none was found, an experience similar to Tallquist's, where excessive doses were not employed. Study of the histological sections shows beyond a doubt, it seems, that the injured red blood corpuscles are taken up by phagocytes which are found in very large number in the spleen and in much smaller number in the liver and bone marrow. In a very short time all the injured cells are removed from the circulating blood, unless, possibly, a few recover and are able to functionate. This phagocytosis of red blood cells occurring in the spleen, liver, and bone marrow in experimental animals is of particular interest ,since Warthin (12) has demonstrated a like occurrence in the spleen, lymph glands, hæmolymph glands, and bone marrow in pernicious anæmia in man. We have, then, produced experimentally an anæmia which may be, and probably is, like primary pernicious anæmia in its origin; in neither is there hæmoglobinæmia, as a rule, though this may exist exceptionally, and in both injured red blood corpuscles are removed from the circulating blood by phagocytes found in the hæmatopoietic organs which possess the double function of forming and "cleaning" the blood.

In embryos Kölliker showed many years ago—and it is now generally accepted—that the liver is the chief and earliest hæmatopoietic organ. Later in fœtal life the spleen also assumes this function and finally the bone marrow becomes effective in blood formation. Toward the end of intra-uterine life, and in the early part of post-natal life the liver and spleen cease forming blood, a function which is reserved solely for the bone marrow. As was noted before, Ehrlich has shown the similarity between the bone marrow of the embryo and that of many patients dying of pernicious anæmia. And Meyer and Heineke demonstrated a like analogy between the blood-forming liver and spleen of the embryo and the same organs in pernicious anæmia. They have also called attention recently to a further point of resemblance of embryo's blood with that seen in pernicious anæmia in the existence of a high color index in each and elsewhere I shall bring forward still another analogy in the presence of "Howell's nuclear particles" in the blood of the human embryo and in that of pernicious anæmia in man. It is evident, therefore, that the work of Meyer and Heineke has marked a distinct advance in the pathology of pernicious anæmia, in that they have shown, so far as it is capable of demonstration at present, that there is not a defective regeneration of the blood in pernicious anæmia (excepting aplastic anæmia), but rather a very great increase in blood formation, the spleen and, in some instances, the liver assuming this function.

In the present experiments it is not possible to prove absolutely that the liver and spleen have reverted to their embryonic condition and taken up the function of blood formation, but it is possible to say that they present the histological pictures seen in the liver and spleen of the rabbit's embryo during the stage of intrauterine life when it is believed that these organs are actively engaged in hæmatopoiesis, and the inference is, therefore, perfectly logical that their function is the same here as it is during fœtal life. That evidence of hæmatopoiesis exists in the spleen in practically all of my experi-

ments and in the liver in only one instance may be explained by the fact that the spleen, which is the last to assume its blood-forming power, is the first to regain it, whereas the liver, beginning its hæmatogenetic function at an earlier period of intrauterine life than the spleen, reassumes it with greater difficulty.

CONCLUSIONS.

1. The anæmia produced in rabbits by the administration of pyrodin (by stomach tube or subcutaneously) is one with a high color index and results from injury to certain of the red blood corpuscles which are then removed from the circulating blood by phagocytes in the spleen, bone marrow, and liver. This resembles the condition found in pernicious anæmia in man.

2. The increased blood destruction leads to increased (compensatory) blood formation.

3. The stimulus to increased regeneration of the blood, whatever its nature may be, leads to heightened activity of the hæmatopoietic function of the bone marrow, the occurrence of myeloid elements in the spleen and occasionally in the liver.

4. The changes occurring in the liver and spleen in the experimental animals are similar histologically, so far as the hæmatogenetic cells are concerned, to those seen in the normal rabbit's embryo at certain stages in its development, and it may be assumed, therefore, that the spleen and liver have taken up their embryonic function, *i. e.*, hæmatopoiesis.

5. The return of the embryonic function is in the reversed order of its disappearance.

6. Hæmosiderosis of the organs occurs as in pernicious anæmia of man.

7. The weight of experimental evidence favors the theory of increased blood destruction (the toxic theory) rather than that of decreased blood formation as the chief factor in the production of primary pernicious anæmia in man.

For illustrations see original publication.

REFERENCES.

1. Meyer and Heincke: Ueber Blutbildung in Milz und Leber bei schferen Anamien. Verhandl. d. deutschen path. Gesellschaft, Bd. 9, p. 224, 1905.
2. Meyer and Heincke: Ueber Blutbildung bei schweren Anamien und Leukamien. Deutsches Archiv. f. klin. Med., Bd. 88, p. 435, 1907.
3. Pozzozzo and Salvioli: Beitrage zur Hamatologie. Moleschott's Untersuchungen, Bd. 2, 1881. (Cited by Gibson and by Howell.)
4. Gibson: The Blood-forming Organs and Blood-formation. Jour. of Anat. and Physiol., Vol. 20, p. 324, 1886.
5. Howell: The Life-History of the Formed Elements of the Blood, Especially the Red Corpuscles. Jour. of Morphol., Vol. IV, p. 57, 1890.
6. v. Voss: Anatomische und experimentelle Untersuchungen über die Rückenmarksveranderungen bei Anamien. Deutsches Archiv. f. klin. Med., Bd. 58, p. 489, 1897.
7. Tallqvist: Ueber experimentelle Blutgift-Anamieen, Berlin, 1900.
8. Rothmann and Mosse: Ueber Pyrodinvergiftung bei Hunden. Deutsche med. Wochenschr., Bd. 32, p. 187, 1906.
9. Reckzeh: Ueber die durch das Alter des Organismus bedingten Verschiedenheiten der experimentellen erzeugten Blutgift-Anämieen. Zeitschr. f. klin. Med., Bd. 54, p. 165, 1904.
10. Bunting: Experimental Anæmias in the Rabbit. Jour. of Experimental Med., Vol. 8, p. 625, 1906.
11. Heinz: Morphologische Veränderungen der rothen Blutkörperchen durch Gifte. Virchow's Archiv., Bd. 122, p. 112, 1890.
12. Warthin: The Pathology of Pernicious Anæmia, with Special Reference to Changes Occurring in the Hæmolymph Nodes. American Jour. of Med. Sciences, Vol. 124, p. 674, 1902.

CLINICAL CONSIDERATION OF OSTEOMYELITIS.[1][2]

A. J. Ochsner, M.D., LL.D., F.A.C.S.,
AND
D. W. Crile, B.S., M.D.,
Chicago

It has seemed worth while to consider osteomyelitis from the standpoint of the clinician because circumstances have favored us with an opportunity of observing an unusally large number of cases suffering from this affliction.

My observations began thirty-four years ago when I served as assistant to Professor Moses Gunn, who treated a very large number of these cases. Following his death, I served as chief assistant to Prof. Charles T. Parkes for a period of three years, and after his death as chief assistant to Professor Nicholas Senn for a period of four years. Each of these surgeons had a great number of cases of osteomyelitis; hence my special interest in this subject.

In my own practice at the Augustana Hospital during the twenty years from January 1, 1899, to January 1, 1919, I have treated 301 cases of osteomyelitis, so that the following views are based upon the treatment and observation of a sufficiently large number of cases to be worthy of consideration. My assistant, D. W. Crile, served in France and England for a period of three years during the recent war, where he had an opportunity of observing several thousands of cases of osteomyelitis due to gunshot and shell wounds, and he likewise is interested in the subject.

Osteomyelitis is a disease, inflammatory in nature, involving bone and having its origin practically always in the medullary tissue, although at times it may originate beneath the periosteum (1), and also as Lejars (5) says: "Frequently there are two foci: one, subperiosteal, and one in the medulla."

Osteomyelitis may be subdivided into the acute infective type, the subacute infective (occurring during the separation of sequestra and including rarifying and condensing processes in the bone), and chronic osteomyelitis in which the infecting organism determines a further subdivision into pyogenic, tuberculous, or syphilitic.

As a matter of fact, the division of infective osteomyelitis into an acute, subacute, and chronic stage, is purely arbitrary, and often can be accomplished only with the greatest difficulty, since the disease is a progressive one. However, as a general rule, the acute stage may be said to occupy the period when a general systemic reaction exists characterized by fever, toxæmia, an increased pulse-rate, intensive pain, always located near the affected part and generally being diffuse over the entire neighborhood. The subacute stage may be said to begin when the toxæmia has been overcome

and suppuration still exists. The chronic stage constitutes that period in which the bone cavities exist.

It is possible for the acute stage to be absent, clinically, so that when first discovered the disease may be subacute or it is possible for both the acute and subacute stages to be negative clinically so that when first discovered, the chronic stage exists. This, however, is due to the fact that the early stages were looked upon as rheumatism, growing pains, or neuritis.

Clinically, the tuberculous and syphilitic forms should occupy a separate classification. They are chronic, although each may be subdivided into an early and a late stage of the disease. Their course, pathology, and treatment are quite different from that of the pyogenic forms so that they will not be considered at this time.

The disease depends for its location and characteristics upon the fact that bone is a rigid and peculiar structure composed of a hard, sparsely vascularized cortex and a soft highly vascular core (the medulla), and a circumferential vascular covering, the periosteum.

All bones contain these three structures. However, they are present in varying proportions. The long bones, such as the femur, tibia, fibula, humerus, and the bones of the forearm contain the greatest proportion of hard tissue and in these the medulla is a true core. This core is transformed into a spread-out, flat structure in the flat bones, but occupies the same relative position to the cortex. If one saws through a bone, the outer layers are found compact while the medulla is found to be composed of an interlacing of thin spikes and spicules having attachment to the cortex. The difference in these two portions is pronounced, the cortex being composed almost entirely of solid matter while the medulla contains large spaces between the spicules, in which there are fat, marrow cells, thin walled blood-vessels, and a considerable amount of blood. However, close inspection shows that the union between these parts is not an abrupt one and that it is often impossible to say at what point the marrow becomes the cortex. However, in the femur and humerus and to a less extent in the tibia a definite medullary cavity exists in adolescent and adult life—the shaft of the bone being hollowed out more completely than the ends. This cavity contains true medullary tissue; fat, lymphoid cells, and hæmoblastic centers. On breaking a long bone transversely, one is able to see that even the densest part of the femur is pierced by tiny canals, each containing a blood-vessel and the larger ones containing lymphoid tissue. These canals are smallest in diameter directly beneath the periosteum where they are about 1/1000 of an inch in diameter and as one progresses toward the medulla, they gradually increase in diameter until at the place where the cortex merges into the medulla they are about 1/200 of an inch in diameter. In the medulla itself they attain a very much greater size (1½). These

canals are nothing more than the tubes in which the blood-vessels lie and are called haversian canals after Clopton Havers, an English physician of the seventeenth century. Each haversian canal is surrounded by a series of concentric columns of bone, which columns are divided one from the other by concentric rings of single, little, thread-like processes which communicate from one cell to the other and with the central tube of the haversian canal. These cells are called the lacunæ and their thread-like processes are called canaliculi. The concentric layers of bone which are really fused into one column and the adjoining columns which are fused together making a continuous plate, are called lamellæ. Between the lamellæ and between the concentric groups of lamellæ, one finds here and there irregular spaces which evidently are a result of the absorption of hard bone. These spaces are called haversian spaces. Virchow (2) says that each of the cells occupying the spaces between the lamellæ is nucleated and Kolliker (3) is authority for the statement that some of the processes from these cells are connected with the periosteum and undoubtedly they also communicate freely with the blood-vessels of the haversian canals.

It will be seen from this survey of the structure of bone that neither the cortex nor the medulla should be considered a crystallized or an inanimate substance. As a matter of fact, one has a better conception of the true nature of bone, if he considers it as a deposit of organized mineral salt between the spaces of a finely-branched system of blood-vessels. Not only is the entire bone permeated by canals containing blood-vessels and living cells absorbing nourishment from these blood-vessels, but lymphatics also most probably exist (4).

The periosteum is also very vascular and is a rather coarse, fibrous membrane, particularly where it affords tendinous insertions. It can be divided microscopically into three parts: the one in immediate contact with the cortex of the bone, consists of strands of fibers containing quite a number of granular corpuscles, particularly in the young animal. These corpuscles are precisely the same as those one finds bordering the haversian canals, and it is possible that they are similar to the bone corpuscles found in the lacunæ.

Surrounding this division of the periosteum is a layer of elastic fibers, and the outer part of the periosteum again becomes composed of white, fibrous strands containing many blood-vessels, which ramify and prepare to enter the openings of the haversian canals of the cortex before they penetrate the elastic layer of the periosteum. These blood-vessels in the periosteum appear to have some muscular tissue in their walls, but the vessels which enter the bone are devoid of muscle (except the nutrient artery). The blood supply of the bone comes also from nutrient arteries which gradually enter the medullary cavity by a hole running obliquely through the compact cortex, and in the long bones the artery generally enters near the middle of the shaft. There are generally a few nutrient arteries entering the bones near their ends, but for the large part the fora-

mina which one sees near the end of bones are for the emission of veins. There are two main nutrient arteries for the femur.

The course of blood through a bone. Arterial blood enters a bone through two routes, the most evident route being via a nutrient artery which, after it reaches the medulla, sends blood both up and down the bone, rapidly dividing into an arborization, the branches of which are short, emptying quickly into comparatively large venous spaces. The other route of arterial blood is via the periosteal vessels, the arborization having already occurred in the periosteum—when following this route the arteries are lost track of almost immediately and capillary vessels conduct the blood through the haversian canals in which it may be said to become venous at once. It seems that this periosteal blood penetrates a very little distance into the bone, compared to the distance that the medullary prenutrient supply does. One can readily see how this comes about when one remembers that the haversian canals have their smallest diameter near the circumference of the bone. The blood issuing from the cut surface of live bone always exhibits the characteristics of venous flow, except when the nutrient artery itself is cut. For these reasons arterial blood, on entering the proper bony circulatory system, loses much of its impulse and becomes static. One may compare the entrance of blood into a bone with that of the entrance of a stream of water into a tank.

Foci of infection. Therefore, any organisms contained in the blood and brought by the blood to a bone, find their first opportunity to rest at the point where they enter the interosseous circulation. This point may be either directly beneath the periosteum or in the medulla at the point where the branches of the nutrient artery enter a blood-space. With the stasis of the blood, the bacteria settle and begin to multiply, undisturbed by a blood current. In this way bacteria which are not virile enough singly or two or three together to make a home for themselves in a more active tissue, are enabled to begin an infective process in the bone. Having multiplied to sufficient numbers, they excite a little inflammation in the delicate cells lining the blood space. These cells swell and leucocytes and fibrin accumulate, shutting off this blood space from the remainder of the circulatory system. This can occur easily because bone encloses the blood space in all directions except its entrance and exit, so that swelling must occur only toward the cavity of the space and can not occur circumferentially. From this little focus toxins and young bacteria disseminate, reproducing and extending this same process. We know that this is true from clinical experience, because the primary focus in acute osteomyelitis is practically always in the shaft and corresponds with the arborization of the nutrient artery as a general rule, occurring most frequently at the places where stasis is greatest, *c. g.*, on the diaphyseal side of the epiphyseal lines and at the cortex of the bone. At both these places the blood-vessels are narrow, and the blood current very sluggish.

It is true that in many cases there seems to be a simultaneous involve-

ment of the subperiosteal region and the medulla, but while this is possible it seems most likely that the process begins in one or other of these locations and rapidly extends through the communicating blood spaces from the medulla to the subperiosteal region, or vice versa. Lejars has noted the frequency of this occurrence and advises that whenever an accumulation of pus is found beneath the periosteum, it should be opened widely, even though no other indication exists—for a medullary abscess is undoubtedly present.

BACTERIOLOGY

Almost any organism may be found in osteomyelitis. By far the large majority of cases are due to the presence of the pyogenic cocci (6), and the staphylococcus is the organism most frequently found. Streptococcus in all its strains, the typhoid bacillus, the pneumococcus, the colon bacillus, the Klebs Loeffler bacillus and others, have all been found in this disease, so that it is quite evident that the disease is not dependent on a specific organism. Neither is there any proof that any particular strain of organism exercises a selective action for the bone marrow.

INCIDENCE OF DISEASE

Osteomyelitis occurs most frequently in the adolescent boy. In a series of 104 cases at the Copenhagen Hospital, it was found that boys were affected three times as frequently as girls, that the bones were affected in the following order: femur, 39; tibia, 31 and humerus, 9; fibula, 7; radius, 4 and ulna, 2. Our experience confirms this sequence.

It is interesting to note the greater frequency of the femur since this bone has more nutrient arteries entering it than any of the other long bones. The long bones are much more frequently involved than any of the others. The infrequent incidence of acute infectious osteomyelitis in the vertebræ is interesting when compared with the incidence of tuberculosis of the vertebræ, and in this connection we would like to point out that perhaps there are many cases of the disease in this region which are incorrectly diagnosed until spinal meningitis is manifested and as such proves fatal.

There is no doubt that trauma predisposes to the localization of the condition at the site of bony contusion. This is the true explanation of the greater frequency of the disease in boys, although the latter are also more subject to exposure.

The disease often follows exanthematous fevers, typhoid fever, pneumonia, acute pleurisy or the presence of a hidden focus of infection anywhere in the body. When following these diseases it is plainly the result of a hæmatogenous transportation of the germ. It is believed that the presence of infected tonsils, infected teeth, disease of the middle ear or sinuses, or chronic appendicitis, are often responsible for the origin of the bacteria causing this disease. In its acute stage, it sometimes is only a

manifestation of a septicæmia or a pyæmia, and in these most serious conditions, multiple foci often exist. However, the disease does not necessarily indicate this grave condition.

PATHOLOGY

Early in the acute attacks the medulla is congested centering about the focus of infection. The periosteum overlying the involved region is hyperæmic, pinkish in color, and heavy with œdema. It feels tense and rubbery, but there is no actual pitting as one sees accompanying inflammation in the subcutaneous tissues. On separating the periosteum from the bone, bleeding is more evident than it is in the normal condition, indicating that the tiny blood-vessels which enter the haversian canals from the periosteum are dilated in their attempt to carry an extra amount of blood to the injured area. One notices this hyperæmia in the cortex itself in some cases when the marrow cavity is opened, for the congestion is quite marked. The normal fat tissue which ordinarily will not flow has a melted appearance and oil may even be seen oozing from the marrow spaces. At this incipient stage one may find no pus whatever, and it is during this time that operation accomplishes the most good, since if the medulla is well drained at this time, the infection may be checked absolutely so that medullary and cortical necrosis do not occur at all. One may discover this stage on the first or second day, but, as a general rule, abscesses are present within twenty-four hours of the onset. The abscess centers about the initial infarct and, if not seen until considerable pressure has been developed in the medulla, secondary abscesses will be found often at quite a distance from the primary focus. It is not at all uncommon to find the entire medulla of the bone full of pus. At this stage of the disease, which may be encountered at any time after the first twelve hours, one frequently finds subperiosteal abscesses as well, which have developed from the medulla through the haversian canals to the subperiosteal region or vice versa.

Epiphysitis.—The epiphysis becomes involved in 12 to 15 per cent of the cases and between the second and seventh day of the disease. When the epiphysis does become involved further growth of bone from the epiphysis may be arrested particularly, if actual separation has occurred.

As a general rule, the disease is limited to the diaphysis, the epiphyseal cartilage acting as a block against extension of the process into the joints. And also the close adherence of the periosteum at the epiphyseal lines checks the extension of subperiosteal suppuration towards the joints. This in counter-distinction to the characteristics of tuberculosis. However, the joints proximal to the acute infection commonly show distention, the distending fluid being a protective outpouring of lymph into the synovia, and the fluid in these joints is very seldom infected. At times this fluid may even show traces of blood and the synovia are œdematous and hyperæmic.

Sequestration.—After frank pus has appeared in the medulla, one hardly expects to prevent the necrosis which generally follows osteomye-

litis. The inflammatory pressure which develops simultaneously with pus in the bones causes a shutting off of the blood and nourishing lymph to certain parts of the involved bone. Thus these parts die, and, after varying lengths of time, are separated from the living parts. The separation of the delicate medullary bone occurs more quickly than does cortical sequestration. Thus medullary sequestra may be loosened after two weeks, while the cortical sequestra generally take from four to eight weeks in separating. The separation seems to be accomplished through the activity of certain marrow cells termed osteoclasts whose function it is to destroy all unnecessary bone. However, it seems that the presence of pus itself has some solvent action upon dead bone and this action is demonstrated by the gradual disappearance of small sequestra which are constantly bathed in pus. This solution of sequestra is a long and slow process which may be aided by chemical stimulation, but surgical removal of sequestra after separation is our practice.

Character of Pus.—As the acuteness of the process decreases, the character of the pus changes gradually, until in the subacute and chronic stages the pus becomes a thin, serous fluid lacking the milky rich appearance of the pus found in the acute condition. The very initiation of the process, however, is generally accompanied by a very thin, almost clear exudate, and this is particularly true when the offending organism is the streptococcus.

Repair.—Reparative processes begin simultaneously with the formation of sequestra which may be single, multiple, or the entire shaft may become a sequestrum. Inflammation stimulates the bone-producing mechanism, and it is not long until new bone begins to appear beneath the periosteum. It seems that this does not come from the periosteum itself but from bone element left clinging to the periosteum and nourished by the vessels of the periosteum. After three or four weeks, the periosteum begins to have a brittle feel much like the crackling of delicate tissue paper, and gradually the layer of new bone nourished by the periosteum assumes a definite thickness and gradually loses its property of being molded until after eight or ten weeks a definite shell of new bone surrounds the old dead bone. This new involucrum is poor in quality. It is honeycombed with spaces through which pus escapes from the neighborhood of the enclosed sequestrum or sequestra. There may be only one small hole through the involucrum but where multiple sequestra are contained, many cloaca are found and often the new shell of bone is so fenestrated as to resemble a very imperfect lattice work.

The new involucrum may be very imperfect in its reproduction of the original bone. Particularly is this the case when entire portions of the shaft have been destroyed and the limb has not been kept in its normal shape by orthopedic appliances. This most often occurs in the upper arm and thigh since in these parts there is only a single bone. In the leg and forearm where a second bone generally retains its shape, deformity does not so readily occur.

New bone is also formed from the medullary region, but this bone is not so important pathologically since from its position it can not surround

dead fragments, and therefore is more homogenous and of better quality than is the subperiosteal bone.

Granulation tissue is more generally found growing from the medullary region than from the periosteal region, and it seems that the chief efforts from the core are directed toward the removal and destruction of sequestra and bacteria, while the efforts of the circumferential tissues seem to be directed toward the reproduction of supporting bone. So far as the pathology of the chronic stage is concerned, it makes no difference whether the acute process has been cut short by surgical intervention or whether nature has accomplished the overthrow of the acute infection. In either case the successful outcome will have been accompanied by the creation of an exit for the pus, so that in the later stages one sometimes finds sinuses leading from the sequestra to and through the skin. If these sinuses are the result of the spontaneous evacuation or of insufficient incisions through the periosteum in draining the abscesses they may be very long and devious. An abscess arising in the medulla at one end of a bone may not find egress from the interior of the bone until it reaches a point quite a distance from its origin. Here it breaks through the cortex to the subperiosteal region, where it may travel still further from the original focus before it makes exit through the periosteum into the fascial planes overlying. This is most likely to occur near the insertion of a tendon and from this point the pus generally travels along the tendon sheath toward the surface where, after a superficial abscess is formed, rupture occurs. Frequently the spontaneous sinus has a direct course to the surface and when this is true it resembles the sinus resulting from surgical drainage. In either event the sinus in the chronic stages is lined by granulation tissue. The granulations which spring from the interior of the involucrum, together with those that line the sinus, pour out a thin chronic discharge. Often the deeper granulations assume characteristics which have led French writers to call them "fongosites." These "fongosites" are overgrown, poorly nourished, œdematous masses— when cut they do not bleed as healthy granulation tissue does. They have a sickly gelatinous appearance and almost always indicate the presence of a sequestrum. When the sequestrum has been dissolved, discharged, or removed, the cavity of the involucrum fills slowly and incompletely with these granulations depending from the lining membrane of pseudo periosteum. These involucral cavities persist for great lengths of time and seldom fill in with healthy tissue. As time goes on the involucrum becomes very dense, and this is particularly true where there have been multiple small cavities and sequestra while the bone at a little distance suffers an atrophy. These two conditions may be seen in the same bone or one or the other may be present alone. The sclerotic condition is termed condensing osteitis while the other is rarifying osteitis.

The pathology of the chronic condition which we have described is generally absent altogether following thorough primary surgical interference, but these changes are so frequently present they must be described.

In considering the pathology of this condition, one must also remember that the overlying soft parts may suffer changes dependent upon infection, disuse or deformity, and likewise contiguous joints may suffer from actual infection or secondary reactions.

SYMPTOMS

Intense pain is the most striking symptom of acute osteomyelitis—pain so severe that the patient's perception of one's intention to touch the limb elicits agonizing shrieks. In severe cases the vibration of a bed from people walking nearby causes pain and the slightest motion of the affected limb is intolerable. The pain may be preceded by, but generally precedes, a high fever, a rigor or a succession of rigors, general toxæmia, and sweating. Soon the affected limb becomes swollen, heavy, and inflamed; the swelling is generally diffuse, as when the femur is involved the whole thigh becomes tense, red and tender. In the leg or forearm the œdema is apt to be most pronounced over the affected bone. The joints are usually not swollen nor tense in the first few hours, but may rapidly fill with serum and result in the appearance of an arthritis; in these cases the limb may be held in the typical positions of the various arthritis.

The temperature rises acutely to very high levels, 103° to 105°, and is of a continuous type with little variation between morning and evening. The patient is generally unable to sleep. The pain is not definitely localized but involves the entire limb. The pain becomes worse on lowering the limb, as one would expect since in this position congestion is increased, and, therefore, pressure on the nerves is increased.

When the bone is involved subcutaneous tapping on it at a distance from the focus will cause pain at the involved area. In case of an abscess or before an abscess is formed, induration may be found over the site, particularly when the subperiosteal focus is present.

In the less acute type the pain is of a constant character, described as an aching, located in the bone, and resembling the so-called growing pains. These cases occasionally show a slight febrile reaction, present one day and absent for an interval. Sometimes the patient will refuse to use the limb as, after use, the pain increases. The subacute type may or may not be painful. There is generally an occasional spell of fever with malaise in the part. This spell may be precipitated by changes in the weather or over-exertion. The surface of the bone may show nodules and irregularities.

The chronic type without sinuses is seldom discovered in boys and girls and in older people often simulates and is probably diagnosed as chronic rheumatism. It is this type that includes the circumscribed bone abscess and bone-cysts. The chronic stage of the acute disease is almost always made evident by the presence of a discharging sinus.

DIAGNOSIS

Acute infective osteomyelitis must be differentiated from acute rheumatic fever which can usually be accomplished by noting that the affection

is extra-articular. When contiguous joints are swollen secondarily, however, the differentiation is not easy. When this condition exists, tapping over the bone at a point farthest from the joint, may cause pain in the bone, while in an acute rheumatic joint, such tapping may be painless *unless the joint be moved*. The presence of a single synovitis argues against acute rheumatism. One finds, too, that the skin overlying the joints is less red and œdematous when the synovitis is secondary to osteomyelitis. The general prostration, while it may be great in both the diseases, is often greater in osteomyelitis. Sometimes the joint contiguous to the osteomyelitic bone can be moved painlessly, but this is rare; one must always differentiate between acute osteomyelitis and an early stage of infantile paralysis. At times this is very difficult. The presence or absence of stiffness of the neck is very important in this differentiation, and whenever two limbs are involved one can safely rule out osteomyelitis, as the disease rarely begins with a double focus except as evidence of a general pyæmia. The acute arthritis of infants generally occurs in the hips and knees and is most often found in nursing babes and may be associated with a gonorrheal ophthalmia or vaginitis (8). In very young children one must always bear in mind the possibility of the presence of scurvy, which can be readily recognized because it affects many joints.

Acute arthritis deformans, especially when occurring in children, may be very difficult to differentiate. Generally the arthritis is multiple, however, the prostration not nearly so sudden, the temperature not nearly so high, and the joints less tense. All these conditions, however, can be excluded by the exact localization of the process outside the joint, and generally on the diaphyseal side of the epiphysis. The condition should not be overlooked in its earliest state when it is usually considered a strain or sprain or contusion, since a history of trauma is frequent.

The X-ray is of little or no value in the diagnosis of the early acute stage except in a negative way, since it may confirm the presence of periosteitis, tuberculous or syphilitic disease, or fractures; when medullary abscess formation has occurred, an excellent X-ray plate may demonstrate the condition, but the diagnosis should be confirmed by one who is thoroughly familiar with the shadows seen in this condition, since they are often very faint and illy defined. The later stages of the disease when bone cavities, cysts and sequestra exist are readily detected by the X-ray.

PROGNOSIS

The prognosis of the acute disease is always grave. When death occurs it is generally during the acute condition, and one finds pyæmia, infarcts in lungs, kidneys, liver, brain and vegetative conditions of the circulatory system as well as multiple foci of infection. These conditions may be the result of an unattended asteomyelitis, but often are concomitant evidences of hæmatogenous infection from some common area.

Early diagnosis with immediate surgical treatment modifies the gravity

of the condition considerably, but one should never predict that a limb with unimpaired function may result.

Often when the focus is virulent and extensive and early treatment has been neglected, when the general reaction is extreme (the type of case which appears to have been "hit by a sledgehammer"), amputation has been recommended as offering the best hope of recovery. In our experience this extreme measure has never seemed indicated, although patients have frequently been sent to Augustana hospital for this last hope. In these cases it has always been possible to change the condition by laying open the periosteum and overlying soft tissues, applying an enormous hot moist boric acid and alcohol dressing covered with a large rubber cloth which serves the purpose of retaining heat and moisture and at the same time acting as a splint, and by applying a therapeutic lamp over this dressing. In a small group of very severe cases it is advisable not to chisel open the medullary cavity of the bone at the primary operation.

With early and thorough surgical drainage one may not expect the process to spread into the neighboring joints, even though synovitis already exists in them. When the focus is close to the epiphyseal line, separation of the epiphysis may follow with the resultant loss of the power of growth from that end of the bone.

At times the extreme virulence of the disease results in the destruction of the osteogenetic powers of the tissues so that the bone will not regenerate. Rarely, the opposite result obtains, *i. e.*, bony overgrowth follows the chronic type.

With early surgical intervention within the first few hours of the disease and in the absence of pyæmia, the focus being well away from the epiphyseal line, one may expect recovery with a functioning limb even in extremely serious cases after a long period of disability and with the remote prospect of several secondary operations for the removal of sequestra and for the obliteration of the sinuses.

TREATMENT

Acute infectious osteomyelitis does not seem to have been recognized until comparatively recent times, the explanation probably being that the abscesses finding their way to the surface, obscured the deep pathology and the cases were treated simply as very grave attacks of boils.

The treatment of the acute condition so commonly practiced until recently with poultices, blisters, fomentations, sedatives, cupping, antipyretics, salves and ointments or manipulation and the healing arts, should be most heartily condemned. The only proper method of treatment is surgical drainage, splitting and reflecting of periosteum over the entire distance and at least two centimeters beyond and on each side, and opening the medullary cavity freely in the area involed. Combined with or following this, the part should be immobilized by splints so arranged that dressings can be done without disturbing the splint. Fomentation in the form

of hot moist dressings seems a valuable adjunct to this procedure, and any of the above mentioned remedies may be employed as accessories without harmful effect except treatment by manipulation. The use of therapeutic lights over the limb is a very valuable adjunct to drainage as they supply heat without the necessity of disturbing the limb. It also seems that the heat waves produced by means of electric light are more penetrating than those produced by the application of ordinary fomentations, hot water bags and electric pads.

OPERATION

The patient is anæsthetized, the limb is cleaned and painted with tincture of iodine. The incision is made down to the periosteum avoiding arterial regions and the nerve-trunks and placing the incision so that it will drain in a dependent fashion without pocketing. The periosteum is freely incised in a longitudinal direction, and if it is not already separated from the bone by the presence of a subperiosteal abscess, it is raised by scraping it from the bone by a sharp rugine such as Ollier devised. The blunt periosteal elevator should not be used nor should the periosteum be stripped roughly from the bone. A sharp, thin-bladed chisel serves the purpose admirably, handled with great accuracy and gentleness.

Rough treatment would result in leaving the osteogenetic elements on the bone and would leave the periosteum impotent to produce new bone. A hole is now made through the cortex with a trephine or a drill or by chisel and mallet, great care being taken to avoid undue jarring of the bone before the operation is begun or during the operation. It may be necessary to make several holes through the cortex, although this is rarely necessary if the point of greatest tenderness is carefully located. In the very early stages one may find no frank pus whatever but the marrow will be oily, serous and œdematous-looking. When this condition or the presence of pus is discovered, a large slab of cortex should be removed, leaving the remaining bone in the shape of a trough. One should chisel sufficient cortex away in both directions from the focus that he may be sure that no secondary focus remains undrained.

The further advantage of this procedure is that any incipient focus, too early to be detected grossly, will be nipped in the bud and will not progress to a destructive stage. The marrow or the exposed area should be removed with a curette and the walls of the cavity remaining may be washed with an antiseptic solution. For this purpose carbolic acid (5 per cent) seems ery efficacious. In virulent infections, pure carbolic acid may be used, applied on a cotton swab and allowed to remain from two to five minutes. After this time it should be diluted with alcohol and the cavity thoroughly washed out with alcohol (95 per cent). In place of using carbolic acid, alcohol alone may be used or ether may be used, and of late Dakin's solution has come into favor for this purpose. Tincture of iodine is excellent. The use of various antiseptic pastes does not seem so successful in the

treatment of the acute stage, although the bismuth, iodine, paraffin paste seems to have a favorable effect. The cavity may be packed with iodoform gauze or plain gauze to prevent the accumulation of a blood clot after operation. The presence of clots during the acute stage is dangerous and may lead to continued suppuration. The use of Carrel's treatment seems to give good results. Stewart and McCurdy declare that $3\frac{1}{2}$ per cent iodine is the best antiseptic and that packing interferes with the formation of a blood clot, in this way interfering with bone repair. It is most likely that the cases in which a blood clot is desirable are not at all the type of case that we are considering since the presence of blood clot in this class of cases almost invariably leads to further septic developments. The wound is left open.

Rosenberg says that streptococcus and pneumococcus epiphyseal suppuration often heals spontaneously and that the treatment in nursing infants should be limited to the opening of abscesses (10). He may, however, have confused the acute arthritis found in infancy with an acute osteomyelitis. One should hesitate in making a diagnosis of osteomyelitis in suckling infants for this reason. In my own cases of osteomyelitis in infants the results have been amazingly good following simple incision.

It seems that Lejars and Robert LeConte (11) agree that it is never expedient to incise the periosteum only, but that in all cases of periosteitis in the adolescent, it is wise to expose the medulla. If no medullary pus is found little harm has been accomplished, while if a medullary focus has been neglected great harm may ensue. My experience has borne out this plan except in the very violent cases described above (A. J. O.) LeConte favors the early removal of all bone and marrow involved and says that regeneration will occur if operation has been done early. This corresponds with the work done by E. H. Nicholls, of Boston (12), who, writing in 1904, thought that the periosteum itself deposited new bone after this operation. There can be no doubt that new bone is generally of good quality, reproducing the shape and function of the bone which has been removed. This is particularly true before the ossification of the epiphyses. The bone-forming elements which remain attached to the periosteum are very active at this time of life. It would seem that in order to understand these results, one must believe that inflammation of the bone loosens the bone-forming elements from the periosteum.

Our observations have convinced me that it is never proper to remove the shaft of a bone during the acute stage of osteomyelitis before an involucrum has been formed, because the resulting arms and legs have been infinitely superior in all cases where there has been a late removal of the sequestra.

Based on the experience of handling many thousand cases of traumatic osteomyelitis during the great war, it would appear that when complete subperiosteal excision of a section of shaft is done within a few hours of inoculation, regeneration occurs with more difficulty and more

often fails to occur than if the same operation is performed later. In traumatic osteomyelitis, excision of a section of shaft bone after inflammation has manifested itself by congestion and thickening of the periosteum, is hardly ever followed by failure of regeneration by the formation of subperiosteal callus. This is particularly true where the bone-scraping technique of Ollier has been followed as described by Leriche (13). When this technique has been skillfully employed, even before the periosteum is inflamed, regeneration almost invariably occurs. These facts argue that the scraping of the bony cortex and inflammation in the same region result in leaving bone-forming elements adherent to the periosteum.

This explanation of the question makes it clear that subperiosteal resections of bone in acute infectious osteomyelitis are not to be feared provided operation is never performed in this condition before the appearance of inflammatory symptoms. This simple fact, *i. e.,* that inflammation always preceded operation in this condition explains the regenerations which Nicholls so fortunately enjoyed but which he attributed to the periosteum itself.

The work of Nicholas Senn, on the other hand, based on the classical experiments of McEwen (14), gave remarkably favorable results. He did not favor the excision of the entire shaft at an early stage, but advocated the operation providing radical drainage, leaving a shell of bone to be dealt with as indicated at a subsequent operation. Nicholls agrees with this idea when the disease is located in either the femur or the humerus, since these bones can not be excised without considerable deformity and shortening resulting. In the case of one of the bones of the leg or forearm, its fellow serves to maintain the length and shape of the limb so that this element does not enter into the question so seriously as it does in the thigh and arm. Taking all things into consideration, it seems that the best treament of the initial stage of the disease is immediate incision through the periosteum, thorough exposure of the medulla, leaving enough supporting cortex to prevent deformity and in such a shape as not to interfere with drainage and leaving a layer of bony scales adherent to the reflected periosteum, the disinfection of the exposed tissues with tincture of iodine, the packing of the cavity with iodoform gauze to be removed on the second or third day, and the provision of free dependent drainage.

This treatment should be instituted immediately on making the diagnosis. One must be careful to avoid the epiphyseal cartilages in doing the operation, since injury to this area results in a hindrance to further bone-growth from the injured end of the bone. When the infective process itself involves the epiphysis there is no other course to adopt, except that of thoroughly clearing away all diseased tissue, since if the surgeon be hindered by timidity, it is possible for the process to extend into the contiguous joint, when amputation may result. It is wise to mention the possibility of the subsequent shortening which one anticipates so that the patient and his relatives may know what to expect.

Supplementing this operative treatment, the limb should be immobilized and local heat supplied, either as fomentation with hot boric acid and alcohol dressings or by using an incandescent lamp so arranged that its heat is directed on to the limb, or a combination of the two methods, the lamp tending to maintain the heat of the moist dressing. The patient should be freely purged, and for this purpose castor oil excels all other drugs. The patient should be given an abundance of good water to drink, and often by giving water in the form of lemonade, aerated waters, mineral waters, or weak tea, larger amounts may be drunk than if only plain water were offered. Large amounts of water provoke a diuresis and this, coupled with the purging, tends to increase the excretion of the toxins which the patient has absorbed from the diseased bone. With this treatment, the infection is rapidly overcome and no further extension of the process should occur.

The after-treatment consists in the removal of the gauze packing on the second or third day, or sooner if the temperature does not fall the day after operation. It is seldom necessary to insert rubber drainage-tubes, if the case has been diagnosed and operated on in the early hours of the disease. However, if the case has not reached the surgeon until the entire medullary cavity is filled with frank pus, or even after the pus has begun to burrow in the soft parts, it is wise to remove the packing after twelve to twenty-four hours and to replace it by one or several drainage tubes, and this type of case will do very well when treated by Carrel's method, with frequent irrigations through many fine tubes, each one leading down to the bone cavity. The wound should be kept open while it heals by granulation from the depths. It is occasionally possible to suture these wounds at their primary operation, leaving a corner of the wound open to permit removal of the gauze pack and for the insertion of a drainage tube, if necessary. If doubt exists as to the wisdom of closing the wound at once, it should be left wide open and closed at a second operation after healthy granulation tissue appears. This should be postponed, however, until the wound has become free from infection, which can be determined by examining the secretion microscopically. One must bear the fact in mind that the presence of bacteria is proof of infection, but that the absence of bacteria microscopically is not sufficient evidence to prove that a wound is sterile.

The cases which are not seen by the surgeon until actual necrosis of a section of the shaft, or, for that matter the entire shaft, present greater difficulty. It is in these cases that immediate excision of the necrotic bone should never be practiced.

I have been impressed with the importance of this rule many times in cases in which it seemed impossible to have any portion of the shaft of a long bone restored to normal. In these cases we employed the treatment described above of splitting all of the soft tissues longitudinally down through the periosteum for a distance of two to five centimeters beyond each end of the area apparently infected and elevating the periosteum from its attachment to the bone for a distance of one centimeter each side of this in-

cision and then applying hot, moist, boric acid and alcohol dressings and placing a therapeutic lamp over all. It has been surprising in many of these cases how small the total loss of bone has been ultimately. The bone which seemed hopelessly dead in many instances seemed to act in the capacity of a bone graft, being replaced to the greatest extent by new bone so that ultimately only a very small portion of the bone was lost.

In one case, a girl of fourteen, in whom the attack was unusually violent, an incision over the entire dorsal surface of the first metatarsal bone showed this structural black from end to end ready to be removed entirely. The treatment described above was employed and in twelve weeks the wound was completely healed without the loss of any portion of the bone. The entire bone served as a bone graft. The healing has been permanent. In my experience this observation has never been repeated to the same extent but a sufficient amount of bone has been saved in a large number of cases to convince me that much value should be placed on this plan of treatment.

The important point to be gained comes from the fact that this treatment directs the lymph stream away from the substance of the bone so that there can be no advancement of the pathologic process, while, on the other hand, all of the natural forces can proceed with the work of restoration.

Whatever can not be repaired by nature can be accomplished surgically later on at leisure when the patient has recovered from the acute condition and when the element of sepsis has been eliminated and the surgeon has to deal only with end-results of the disease.

CHRONIC OSTEOMYELITIS

The experience of the war has been of great value in furnishing experience in the treatment of chronic osteomyelitis, although conditions are not exactly parallel. The important lesson universally learned corresponds with the experience of the few civilian surgeons who had a large experince with chronic osteomyelitis before the war, namely: (1) that in order to succeed one must remove absolutely all dead substance. In war surgery this means foreign substances in addition to sequestra which are alone to be considered in civil practice. (2) Provision must be made for filling the defect after all foreign bodies and dead bone has been removed and every portion of the remaining cavity has been throughly freed from infectious material.

Methods of closing the defect. My earliest experience with these cases was as an assistant of Moses Gunn, in whose clinic we treated a great number of cases of chronic osteomyelitis.

After removing all sequestra and producing a smooth cavity he tried to obtain healing from the bottom by keeping the external wound open by means of a paraffin plug.

This plan proved very satisfactory although somewhat tedious. I also had an opportunity of observing many cases treated in the clinic of Charles T. Parkes who was my surgical chief following the death of Professor Gunn. The same plan of treatment and the good results continued.

For a number of years following this experience, I assisted Nicholas Senn in the treatment of many of these cases. After thoroughly removing all sequestra and infectious matter and smoothing the cavity in the bone, he chiseled away a sufficient portion of the involucrum to permit the edges of the wound to unite without the slightest tension.

Then the cavity was carefully disinfected with 5 per cent carbolic acid and throughly dried; then finely cut, decalcified bone chips, which had been preserved in 1:1000 corrosive sublimate solution, were dried and sprinkled with iodoform powder and carefully packed into the cavity in sufficient quantity to fill the cavity barely full. Then the edges of the wound were carefully sutured so that the coaptation was perfect. A very large dressing and immobilization splints completed the operation. The results were excellent. The reason why the method has not received more extensive adoption lies in the fact that few surgeons work with sufficient accuracy to carry out every detail of this procedure which is necessary in order to prevent the breaking down of the implanted graft. Moreover, the simpler method introduced by Max Schede about the same time brought identical results. Moorhof introduced a plug about the same time which we used with equally good results in a few cases but which we abandoned again because the results seemed no better than with Schede's method.

This method consists in the steps described in connection with Senn's method to the point of filling the cavity, the technique then being as follows:

The cavity is left empty and the wound is closed by means of a double row of continuous catgut sutures the first row acting as tension sutures and the second row as coaptation sutures. An Esmarch constricting bandage is left undisturbed until the very large dressing supported with a number of splints has been applied and the patient has been returned to his bed with the limb elevated in order to prevent the cavity to fill moderately with a blood clot which may remain undisturbed because of the character of the dressing until it has become throughly organized.

In each of the three methods described last the element of absolutely preventing any disturbance of the clot filling the cavity in the bone is of the very greatest importance. The failure to appreciate this fact has resulted in most of the bad results following the use of these methods.

In cases in which there is not sufficient tissue to cover the cavity the method described by Emil Beck of carrying what skin is available toward the bottom of the cavity without tension has given very satisfactory results.

In a number of cases in which the healing has been too slow, we have covered the granulating surface with Thiersch grafts. It is amazing to see how these troughs will fill up after covering the granulations with Thiersch grafts. Occasionally we have loosened long lateral flaps and have united

these in front over the defect in the bone and then we have covered the defects on each side by means of Thiersch grafts.

RECURRENCE

In our cases recurrence has seemed to be due most commonly to the fact that during the primary treatment the source of infection was overlooked so that the patient suffered from a re-infection rather than a recurrence in the usual sense of the word.

Many of these patients state that they had a cold or a sore throat or a toothache just before their osteomyelitis recurred. Upon making a careful examination one finds a buried tonsil containing an abscess or an abscess at the root of a tooth or some other focus of infection. For thirty years we have removed these infected tonsils and roots of teeth in many cases in which recurrence had occured, and the patient has repeatedly remained free from trouble for a number of years.

Trauma is another common cause of recurrence. Apparently some slight injury determines the return of infection to a bone that has previously been the seat of osteomyelitis.

Sugar. Patients consuming large quantities of sugar are subject to the developement of furuncles and carbuncles and occasionally this seems to be an element in determining the occurence of recurrent osteomyelitis.

Cold and exposure. We have seen a number of recurrences following exposure to cold and wet. In these cases, however, there has been an infection of the tonsils, the sinuses or the air passages.

We have not been able to associate osteomyelitis with the occurence of intestinal disturbances although *a priori* one would suppose that this might be a source of infection.

CONCLUSIONS

1. An early concise diagnosis and immediate surgical treatment is of the greatest importance.

2. The operation should invariably consist in splitting the periosteum for a distance of 2 to 5 centimeters beyond the area of pain upon pressure in the bone in each direction.

3. The periosteum should be loosened from the bone for a distance of 1 to 2 centimeters on each side of the incision.

4. In extremely severe cases this should be the extent of the primary operation.

5. In less severe cases ultimate healing can be hastened by carefully opening the medullary canal at the point previously located because of pain upon pressure.

6. Care should be employed to prevent traumatizing the tissues by rough chiseling.

7. Moist hot antiseptic dressing with fixation of the extremity and with the use of electric light treatment increases the comfort and facilitates healing.

8. The shaft of a long bone should never be removed until a good involucrum is formed.

9. In late cases or in secondary operations upon cases treated as above in the acute stage, every particle of dead tissue must be removed.

10. At this operation some definate plan must be carried out to facilitate closing the defect.

11. Skin grafting is of great value in many cases.

12. Local foci of infection such as abscesses of tonsils or teeth or sinuses, should invariably be eliminated at once upon undertaking the treatment of patients suffering from osteomyelitis.

REFERENCES.

1. Coplin: Manual of Pathology, p. 718.
1a. Quanin's Anatomy, Vol. 1.
2. Virchow: De peritiori ossium structuria, p. 17, Fig 6.
3. Kolliker: Wurzb. Nat. Ztschr., Vol. 1, 296.
4. Cruikshank: Anatomy of the Absorbing Vessels.
5. Lejars: Urgent Surgery, pp. 550-554.
6. Delafield and Prudden: Textbook of Pathology, p. 886.
7. Alfred C. Wood: Acute osteomyelitis in children. Penn. M. J., 1918, December.
8. Clement Lucas: Quoted by Sir Wm. Osler. The Principles and Practice of Medicine, p. 378.
9. Powell: Carbolic acid in surgery. Med. Record, 1899, Iv. 372.
10. Rosenberg: Osteomyelitis in suckling infants. Muenchen. med. Wchnschr., 1911.
11. Robert LeConte: Acute inflammation of long bones. Boston M. & S. J., 1911, June 1.
12. E. H. Nicholls: J. Am. M. Assn., 1904.
13. R. Leriche: Treatment of Fractures. Univ. London Press, Ltd., 1918.
14. Nicholas Senn.

A RAPID METHOD OF PNEUMOCOCCUS TYPING.*

Wade W. Oliver,

Brooklyn.

Because of its prognostic value and also because it is necessary for specific serum therapy, a number of methods for the determination of pneumococcus types have come into use.

The standard methods up to 1917 are reviewed by Blake,[1] special emphasis being placed on intraperitoneal inoculation of the mouse with washed sputum and agglutinin and precipitin tests of the peritoneal exudate. Avery[2] reports a rapid cultural method for the determination of pneumococcus types in lobar pneumonia. By the use of a meat infusion broth with 1 per cent. glucose and 5 per cent. rabbit blood, sufficient growth usually is obtained within five or six hours for precipitin test made with the clear fluid.

In order to still further save time, Mitchell and Muns[3] describe a method for detecting pneumococcus precipitinogen in sputum, 5 c.c. of which are ground in a small mortar with sand until a paste is formed. Then 10 c.c. of normal salt solution are slowly added and stirred into the mixture and after three or four minutes, the dissolved sputum is pipetted off, the solution centrifugalized at 2,200 revolutions per minute for from five to ten minutes, and a precipitin test made with the clear fluid.

Krumweide and Valentine[4] suggested a coagulation method for the rapid determination of precipitable substances in the sputum. As in the method of Mitchell and Muns, considerable quantities of sputum are required, a decided objection against the method in certain cases in which only small amounts of sputum can be obtained. From 3-10 c.c. of sputum in a test tube are placed in boiling water until a "more or less firm coagulum results. The coagulum is then broken up with a heavy platinum wire or glass rod and saline is added. Just enough saline should be added so that, on subsequent centrifuging, there will be sufficient fluid to carry out the test." The tube is again placed in boiling water for several minutes, after which centrifugalization is employed. The supernatant fluid, which is the antigen, is then floated over 0.2 c.c. of undiluted antiserum. "If a fixed type was present in the sputum, and should the sputum have been rich in antigen, a definite contact ring is seen in the tube containing the homologous serum. With sputums less rich in antigen, the ring may develop more slowly and it will be less marked."

The test that I describe is based on the solubility of the pneumococcus in bile. Taking advantage of the fact that in a typical case of lobar pneumonia the infecting type of pneumococcus is often found in predominating numbers in the sputum of the patient, 1 c.c. or less of such sputum, immediately on its receipt in the laboratory, is stirred in sterile salt solution and bile added. After the protein has gone into solution in the bile, the mixture is filtered and a precipitin test is immediately made with the filtrate. The series on which this test was used comprises twenty-five cases. On an aver-

age, the time for effecting a typing was from twenty to thirty minutes. The results follow:

METHODS EMPLOYED AND PNEUMOCOCCUS TYPES

Cases	Pneumococcus Types		
	Rapid Precipitin	Avery's Method	Mouse
1	3	3	—
2	3	2	—
3	1	—	—
4	2	—	—
5	Negative	Negative (streptococcus)	Negative (streptococcus)
6	3	3	—
7	1	1	—
8	2	—	—
9	1	1	—
10	Negative	4	4
11	Negative	4	4
12	Negative	4	4
13	Negative	4	4
14	Negative	4	4
15	3	3	3
16	1	1	1
17	Negative	4	
18	Negative	4	
19	Negative	4	
20	Negative	4	
21	Negative	Negative (streptococcus)	—
22	Negative	4	4
23	Negative	Negative (streptococcus)	Negative (streptococcus)
25	Negative	Negative (streptococcus)	Negative (streptococcus)

We note that four cases belong to type 1, three to type 2, three to type 3, and eleven to type 4.

A direct smear of the sputum, a selected fragment of sputum being chosen, is stained by Gram's method, as examination of such a smear is of distinct value in determining the presence of the pneumococcus as well as its relative numbers in the sputum. Next 1 to 1.5 cm. of sputum are placed in a clean test tube which contains a glass rod. Normal salt solution is then added, small quantities (0.1 to 0.2 c.c.) being added at a time and vigorous stirring with the glass rod following the addition of each portion of solution. After from 0.5 to 0.8 c.c. of salt solution have been stirred into the sputum, from three to five drops of undiluted ox bile are added and the mixture thoroughly stirred. The amount of salt solution to be added is dependent on the consistency of the sputum, the endeavor being to obtain a fairly homogeneous specimen of a sufficiently fluid nature to admit of filtration or centrifugation. The tube is then immediately placed in a water bath, in water at 45 to 48 C. for ten to twenty minutes, which suffices for solution of the pneumococci by the bile. The fluid is then immediately filtered. For filtration, a filter paper listed as "Eimer and Amend Best White Filter Paper No. 15" has been employed. The filter paper mounted preferably in a small funnel having a long stem, is first moistened with a small amount of normal salt solution. Filtration at ordinary atmospheric pressure will usually be somewhat slow. By the use of a suction pump and a small amount of negative pressure, the process of filtration is greatly facilitated. It has been my experience that the filtrate so obtained is clear and colored to only a slight extent by the bile.

In lieu of filtration, centrifugilization may be employed. After the pneumococcus protein has dissolved in the bile, the mixture is placed in a centrifuge tube and a small amount of cotton, with the fibers loosely united, is placed on the top of the fluid. Centrifugalization is commenced at low speed and the speed is gradually increased up to about 2,000 revolutions per minute. As the speed increases the cotton is pulled down to the bottom and assists appreciably in clearing the solution.

Of the filtrate or centrifugate, 0.3 to 0.5 cm. are now pipetted into each of three small tubes. To the first tube is added one drop of undiluted type 1 pneumococcus antiserum, to the second tube is added one drop of undiluted type 2 antiserum and an equal quantity of type 3 antiserum is added to the third tube. In case of a doubtful reaction, the addition of another drop of antiserum may be indicated.

When a positive precipitin test is obtained, a clouding occurs in the fluid almost immediately on the addition of the specific antiserum. The test becomes still more marked if the tubes are immersed for from ten to twenty minutes in water at 48 C. Following this, if the tubes are placed in the icebox, the positive tube, after several hours, will show a sedimentation of the specific pneumococcus proteid, the supernatant fluid appearing clear.

In all of the cases in which a positive precipitin test for one of the first three types of pneumococci was obtained, the results were identical with those obtained by the Avery method. In five instances, the sputum of the same patient was typed on several consecutive days, with identical results, in each case the rapid precipitin test checking with the Avery method. In the fifteen cases in which the rapid precipitin test was negative, the Avery method revealed a type 4 pneumococcus in eleven of the series, and in the remaining four cases, a streptococcus. In this series of fifteen negative tests, intraperitoneal inoculation of mice with washed sputum was employed in ten and in each instance the results were the same as those obtained by the Avery method.

The necessity of obtaining a true specimen of sputum from the deeper air passages as free as possible from saliva was strikingly brought out in case 8. The first specimen was not sputum, but saliva, and the rapid precipitin test and the Avery method showed a type 4 pneumococcus (probably from the mouth). A blood culture the following day revealed a type 1 pneumococcus.

In the cases, the parallelism between the results of the rapid precipitin test and the Avery method is striking. It would seem to suggest that when a typical pneumonia sputum is received on which the rapid precipitin test fails to reveal a "type," immediate intraperitoneal injection of a white mouse with the washed sputum would be indicated. On the other hand, when the rapid precipitin test is positive, it would seem justifiable, so far as we have gone, to accept the results for clinical purposes, especially in cases in which the rapid precipitin test reveals a type 1 pneumococcus, in which case immediate administration of type 1 antiserum would be indicated.

Two of the patients in whom the rapid precipitin revealed a type 1 pneumococus were exceedingly ill on admission and in both instances the sputum was "typed" within half an hour. In both instances the prompt administration of type 1 pneumococcus antiserum was succeeded by recovery.

Microscopic examination of direct smears of the sputum is of distinct value in that it gives an idea of the relative numbers of pneumococci in the sputum. The greater the number of pneumococci in a given sputum, if they be of one of the first three types, the greater will be the amount of pneumococcus protein dissolved by the bile and the more rapid and clean-cut will be the precipitin test obtained on addition of the specific antiserum. Hence the sputum chosen for the test should be that portion which conains pneumococci in the largest numbers, this being usually the portion which is most streaked with blood or most purulent.

SUMMARY

The method described is a rapid precipitin test of filtered pneumonic sputum, to which bile previously has been added. By this method a "typing" of the pneumococcus may be effected within half an hour after receipt of the sputum.

HYPERPLASTIC PYLORIC STENOSIS OF INFANCY*

DUDLEY W. PALMER, M. D., F. A. C. S.

Cincinnati

The literature of congenital pyloric stenosis, frequently miscalled hypertrophic, has been so voluminous and the symptomatology has been so ably presented in recent papers by Porter, Holt, Downes, Scudder and many others, that it is quite unnecessary to review it at this time. We have all heard of the young man's prerogative of drawing conclusions from a few cases. I am asserting my claim to this privilege, and with your indulgence, shall relate a few experiences and draw a few conclusions from twenty-seven cases I have observed of pyloric stenosis in infants.

In the diagnosis of this condition the gastric wave is, I believe, the most important single symptom since it is either present, or a history of its former presence can be obtained. These waves may be stimulated by a feeding, and when thus seen are a definate evidence of pyloric or duodenal obstruction. At the approach of the terminal stage of emaciation, the wave may be absent, as stomach atony and dilation eliminate muscular contraction that is visible through even the thin abdominal walls of the starved infant. All are familiar with these waves that arise under the left costal arch and seem to travel slowly across the epigastrium to the pyloric area, diminishing in size and fading away when this is reached. In the more marked case, during the period of good muscular tone, there may be a wave beginning just as the preceeding one reaches the pylorus. These waves are as a rule, accompanied by the usual evidences of abdominal pain seen in infancy; also they are most active just preceeding the characteristic explosive vomiting. In all but two cases in my series, these waves have been present. In one case of merycism or rumination, an operation was done because of erroneous preoperative diagnosis. The patient was a six months old baby of about birth weight. The vomiting was typical. The great emaciation led us to believe that gastric atony accounted for the absent waves. In the second of these two "waveless" cases, the explanation of atony was correct. I believe that the greatest value of the X-ray in these cases is not as an aid in the making of a diagnosis, but in the demonstration of the condition of the muscular wall of the stomach, thus giving visual data for prognosis. A stomach showing very weak or no gastric waves warrants the assumption of a poor prognosis and the urgent need of emergency methods. I have seen cases in which unquestionably real harm has been done an infant because of delay, due to the report by the roentgenologist that the opaque meal had passed on from the stomach to the small intestines.

Persistent gastric waves seen in a vomiting infant led to only two errors in pathologic diagnosis, although the value of this sympton in making a surgical diagnosis has been 100 per cent. One error occurred in an infant

of eleven days, who had a complete atresia of the duodenum at the juncture of the first and second portions, that is, above the papilla. The child was in extremis and died. The second child seen early this summer was six months old, its weight at birth was 8 pounds 1 ounce, at operation 8 pounds 12 ounces. There had been more or less continuous or daily vomiting of food and gastric secretions, at times explosive, with very indistinct waves seen by the last pediatrician in attendance. The obstruction was only relative as food was always present in the stools, and the weight fluctuated up and down from birth weight. Most excellent advice as to feeding had been given. No blood had been vomited, and there was no history of blood in the stools though test had not been made. The preoperative diagnosis, here too, was pyloric hyperplastic stenosis of a mild form. On introduction of the exploring finger, I was somewhat chagrined not to feel an olive-like tumor at the pylorus. Delivery of the pylorus showed a normally soft unthickened pylorus with a tag of omentum plastered to the duodenum about 1 cm. distal to the vein. Other adhesions were present narrowing the pylorus; the area under the omental adhesions was typically "stippled" and scarred. The duodenum was so small that I hesitate to say there was crater-like induration. We were of the opinion that the child would not stand a gastro-jejunostomy, so a pyloroplasty was made, cutting through the mucosa from the duodenum well into the stomach and closing to make the line of the wound at right angles. Bile was vomited once and for four days the child did well and gained. Then it began to vomit more and more of its feeding, until by the tenth day it was evident that further interference was indicated. I almost hoped the family would relieve my responsibility by refusing a second operation, but they did not, and a posterior gastrojejunostomy was performed. The child gained rapidly and consistently, doubling its weight in three months.

So far as I have investigated the rather scant literature of infantile duodenal ulcer, I did not find any reference to operation in so young an infant. The gastric wave symptom therefore is of true surgical diagnostic value.

I would like to call attention to an error almost universally made in terminology by writers who call this condition hpyertrophic. I have had but one death due to this congenital anomaly and this in an unoperated infant, but I have seen material from several cases. The histologic picture is not hypertrophic but hyperplastic. The individual muscle fibers are not particularly increased in size, but there are more of them. Added to this is a varying amount of edema, and it is this edema that puts the finishing touch to the picture in the majority of the cases.

No doubt there will always be differences of opinion between internists and surgeons as to a certain group of these cases, namely, the so-called spasm group. My own belief is that there is no such clinical entity as the "pyloric spasm of infancy," and that every case in which the symptoms are intermittent or remittent in character, is at least a mild case of true hyperplastic

pyloric stenosis. This edema is a variable quantity producing by this varia-
tion the symptoms of spasm the medical man so delights to treat with bella-
donna veratrum-viridi and other drugs. There is just as much reason to
say that the enlarged prostate, that in the "drunken spree" produces acute
urinary retention, is due to a spasm. Similarly the obstruction is not a true
stenosis of the lumen of the pyloric canal any more than of the urethra in
prostatic hypertrophy. These obstructions are peri-ureteral and peri-
pyloric. The above explanation is satisfactory for many of the observed
symptoms such as the primary period of a few days or weeks without seri-
ous vomiting. It puts all these cases with similar symptoms into one group
with a material basis instead of forcing upon us the necessity of evolving
two groups to explain an otherwise simple condition.

I want to call attention also to the fact that no reference was found in
the literature to an instance in which the surgeon opened up a "spasm
case" by mistake and found a "spasming pylorus." On the other hand, a
sad number of cases were found in which the infant had been treated medi-
cally for spasms until death from starvation occurred or the case became
a grave surgical risk. Surgeons owe it to these helpless children to clarify
the atmosphere and put this syndrome on a material rather than an elusive
nervous-spasm-theory basis. Hutchinson's statement that when these in-
fants get bad enough "they always turn the corner and get well" is not a
safe rule for procedure in view of what surgery now can offer.

Before discussing the points in the operation, I shall say a few words
with reference to the time the operation is indicated. Many patients who
present rather acute symptoms do not need operation. Careful attention to
the feeding, increasing the alkali intake, attention to the bowels, gastric
lavage, and attention to air swallowing during nursing all are items of well
known value to the good pediatrician. Watchfulness in these matters may
tide the infant over a period when the edema is symptom-producing.

Sauer, in July, 1918, was perhaps the first formally to report the use of
paste feeding in congenital pyloric stenosis, though I had seen it used fre-
quently before this in some cases in which I was interested. The paste feed-
ing will unquestionably produce striking results in many cases, but I do not
believe it will prove a cure all. Porter, in discussing the matter at the
meeting of the American Medical Association, 1919, said: "He may use the
thick feeding with an assurance that a proportion of cases will respond with
complete restoration of digestive and nutritional function, and for stubborn
cases there is still left the brilliantly successful operative method of Fredet,
which, used early enough, ought to obtain 100 per cent. of cures." This last
clause, in my opinion, requires and assumes a very close co-operation be-
tween the pediatrician and the surgeon to insure justice to the child and to
each other.

A period of waiting may be desirable until normal dilatation of the canal
occurs through physiologic use of the parts, and to permit an increase in
the muscular development of the stomach to propel the food along its course.

While waiting it should be remembered that a child of two weeks weighing seven pounds is in far better condition than a child of two months weighing a pound or so more, and the younger infant can lose a pound with less risk. A child of about one month even moderately well nourished, if it is holding its weight, can be treated paliatively for a couple of weeks while a little later a stationary weight may not warrant palliative treatment. The economic condition and intelligent co-operation of the mother also affect the decision with regard to treatment. Needless to say the child whose vomiting is excessive, whose stools are without food content and who is steadily and rapidly losing weight, is a case for urgent surgery. Other evidences point to such urgency, such as loss of skin elasticity, sunken fontanelles, concentrated or even suppressed urine, stupor and disappearing displays of hunger. Finally, it may be said that an operation is safer than the care of a poor pediatrician, even though the symptoms are mild; it is also safer than the average unintelligent though well meaning treatment by the parents.
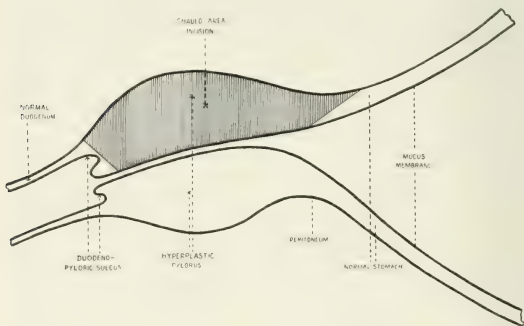
The Fredet or so-called Ramstedt operation has undoubtedly lifted the surgery of congenital pyloric stenosis from an extremely hazardous group to the realm of comparatively safe surgery. Operative risks and operative mortality no longer incline one to delay; on the contrary the operation can be advised to relieve the more mild symptoms and thus shorten and remove the worry of the parents. I have been interested in watching several patients for whom operation was refused, the condition not being urgent. These patients are still subject to attacks of gastric pain and distress with eructations, and are an untold worry to the parents. Undoubtedly, however, some children are left without any symptoms after the original attack subsides.

Practically every patient coming to the surgeon is in a marked state of acidosis and dehydration. I have adopted the principal that a further delay

of twenty-four hours in which to prepare the infant is the wisest precedure. The preparation consists of alkaline gastric lavage, alkaline colon flushes (one or two) ; enemas of from 30 to 75 cc. every three hours and from 30 to 50 cc. of normal salt solution subcutaneously at three hour intervals, thus correcting a suppressed urinary secretion and improving the shrunken, dried up appearance. The subcutaneous injections may be used after operation for about twenty-four hours by which time nourishment is given freely. Feedings are continued up to the time of operation, in the hope that some part of the retained food may be passed on from the stomach; a thorough gastric lavage is given just before operation.

A number of cases of hyperplastic pyloric stenosis is associated with thymus enlargement, producing very embarassing symptoms, have occurred in my practice and I know of several "thymic deaths" following operations for pyloric stenosis in infants. Two years ago Ransohoff reported such a case with postmortem finding in which death occurred about seven months after a perfect operative result. The associated enlarged thymus in my experience has been more frequent than the incidence of enlarged thymus in the average infant, and the possibilities are so serious that a routine x-ray picture should be made of the chest before operation, and followed by treatment if the enlargement is found. You have all, no doubt, noticed the frequency of the references in the literature to sudden deaths following operation for pyloric stenosis.

It is scarcely necessary to call your attention to the fact that everything must be done in the operating room to conserve the body warmth and to expedite procedures. Cleansing the skin thoroughly with alcohol is sufficient. The extremities must be fastened to the table as otherwise their movements on the table may be disquieting. Ether is best for anesthesia; very little anesthetic is needed and a few drops of ether make a change from semi-consciousness to a too-deep anesthesia, from squirming and possible evisceration to suppressed respiration. I have not yet tried local anesthesia. A high right rectus incision extending well up to the costal border, of from 2.5 cm. to 3.75 cm. in length, is a great advantage, because the normally low hanging liver controls a tendency to evisceration; later the liver acts as a support should the integrity of the wound be threatened by the secretion of serum during the healing period. Two fingers are introduced and the liver is pushed up. By wiggling the fingers very much as Dr. C. H. Mayo suggested many years ago for finding an appendix, an olive shaped mass is palpated. This tumor is lifted to the surface and its most avascular area is incised longitudinally down to the mucosa. Because the shape of the infant's pyloric aperature on the duodenal side is very much like the cervix in a vagina, it is necessary to be extremely careful to avoid opening the sulcus or gutter surrounding the pylorus. Such a technical error adds greatly to the risk, since a plastic operation or a gastrojejunostomy then unfortunately becomes necessary. Frequently one cannot avoid cutting a small vein and as every drop of blood counts, it has seemed wise to control this with

a hot tab of gauze applied directly to the bleeding point for a few minutes; this time is well spent, I believe, as catgut ligatures bite through this edematous, butter-like tissue. The incision can be extended well upon the stomach side of the pylorus without great risk, but it is much safer to refrain from attempting to cut the last few muscle fibers on the duodenal side. If a few fibers are left, spitting up or regurgitation of some food may occur; this is temporary and not alarming as the larger part of the food is retained and the explosive vomiting is controlled.

The pyloric tumor is returned to place without further attention and the liver dropped down behind the incision. A layer suture of the abdominal wall, using a fine catgut (No. 0 chromic catgut) with silk worm figure-of-eight fascial sutures has given the best results. No. 1 or No. 2 plain or chromic catgut is too large to be taken care of in the abdominal wall of these starved babies. Even with extreme detailed attention, a rather large percentage of patients have a serum discharge that necessitates frequent dressings for a week or ten days. None of the wounds in my cases has had real pus form and none has failed to heal tightly without hernial tendencies.

```
Patients with congenital hyperplastic pyloric stenosis..........27
Patients operated upon.......................................23 (85.18%)
        Fredet operations—20
        Gastro-enterostomy—3
Patients not operated on......................................... 4 (14.81%)
        1 died before operation could be done.
        2 improved with palliative treatment (mild cases).
        1 refused operation and has occasional symptoms.
Males .......................................................... 79%
First-born ..................................................... 58%
Average age of patients at onset of symptoms................ 14 days
Average age of patients when seen or at operation........... 62 days
Average duration of symptoms................................ 48 days
Thymus enlargement proved to exist in patients operated on.... 26%
Examination for palpable tumor positive ...................... 37%
Examination for palpable tumor doubtful ...................... 18%
Examination for palpable tumor negative ...................... 45%
Waves visible ................................................. 95%
Patients of weight less than birth weight..................... 61%
```

BIBLIOGRAPHY

1. Downes, W. A.: The operative treatment of pyloric obstruction in infants. Surg., Gynec. and Obst., 1916, xxii, 251-257.

2. Holt, L. E.: Medical versus surgical treatment of pyloric stenosis in infancy. Jour. Am. Med. Assn., 1914, lxii, 2014-2019.

3. Hutchinson, R.: Congenital pyloric stenosis. Brit. Med. Jour., 1910, ii, 1021-1024.

4. Lewitt, W. B., and Porter, L.: Pyloric obstruction in infants with muscular hypertrophy at the pylorus. Jour. Am. Med. Assn., 1912, lvii, 256-259.

5. McClanahan, H. M.: Duodenal ulcer; report of a case in which operation was followed by improvement. Jour. Am. Med. Assn., 1916, lxvii, 1270-1271.

6. Palmer, D. W.: Hyperplastic pyloric stenosis. Ann. Surg., 1917, lxvi, 428-435.

7. Porter, L.: A retrospect of fifteen years' experience in the treatment of hypertrophic obstruction in infants. Arch. Ped., 1919, xxxvi, 385-397.

8. Ransohoff, J. L., and Woodbury, P. G.: Operative cure of congenital pyloric stenosis. Jour. Am. Med. Assn., 1917, lxvii, 1543-1544.

9. Sauer, L. W.: The use of thick farina in the treatment of pyloric stenosis. Arch. Ped., 1918, xxxv, 385-400.

10. Scudder, C. L.: Stenosis of the pylorus in infancy. Ann. Surg., 1914, lix, 239-257.

COMPLICATIONS AND END RESULTS OF BILE DUCT INFECTION.*

J. EDW. PIRRUNG, M.D.,

Cincinnati.

It is generally agreed that most of the diseases found within the bile passages are due to infection direct from the duodenum or infections carried by the blood and lymph streams to the liver. A considerable number of these infections come through the portal circulation, which is the great absorptive and drainage system of the intestinal tract. A previous typhoid is suggestive, a long history of constipation, obstipation, or hemorrhoids predisposes to bile passage infections. Fermentations and intoxications due to an increased bacterial growth in the intestinal tube give an increased work to the liver cells, consequently all the bacterial can not be burnt up in the liver; some find their way into the bile passages and to the gall-bladder.

Sir Berkley Monyhan has observed the frequent occurence of distentions with in the duodenum, infection of its contents, duodenum inflammation, duodenal ulcer and gall-stone in the same patient. Sir William Lane advanced a step farther. He states that duodenal distention is the result of delays to the passage of the fecal current. Infections then occur in the intestinal canal, inflammation, ulcer, and gall-stones are the result. Bacteria and their products being absorbed are carried by the blood and lymph streams to the liver, there many of them are destroyed, others pass out into the ducts, infecting the bile. The deposit of altered secretions of the liver forms stone in the gall-bladder and bile passages. Infections, inflammation, distentions, altered secretions and the consequent lowered nutrition, with blood infections causes ulcers in the stomach and duodenum. The bacteria usually found in the bile passages are bacilli typhosus, bacilli coli and the pus producers. Persons leading a sedentary life, women past middle life, repeated pregnancies, dietary indiscretions and chronic infections in any of the abdominal organs predisposes to gall duct infections. The symptoms when stones are present and are passing through the bile passages are well known and need no comment.

The History.—The early history is the most important in diagnosis before colic occurs. Occasionally hepatic colic seems to be the first evidence of gall duct trouble. However, on close questioning in such cases, you will bring out the story of a previous stomach trouble, bilious spells, fulness or distention preceding the attack of colic. When a patient comes to you with a history of long and continued dyspepsia, with nausea, fulness in the epigastrium, rightside bloating, constipation marked, occasional bilious attacks with temperature, severe pain in the right side running toward the middle line, pain temporarily relieved by vomiting (vomitus containing no

blood), a presumptive diagnosis of infection of the bile passages can be made.

Examination of the stools during the acute attacks may also help in the diagnosis. There may be a temporary absence of bile in the stool due to stone obstruction or to the congestion and swelling of the mucosa of the ducts. Gall-stones are sometimes recovered from the stools. The above are the usual early symptoms of a persistent infection of the bile passages. When physical signs occur you are dealing with an end result of infection. The failure to elicit from the patient the symptoms of infection or stone in the bile passages is usually due to an incomplete questioning. These patients will frequently give you the suggestion of gall-bladder disease in their history. You do not require jaundice, severe pain, a tumor mass, septic fever, itching, vomiting and clay-colored stools to make the diagnosis. These are the complications of infections. The time for permanent relief may be far past when one or more of these occur. They usually mean persistent obstructions of the cystic or common ducts by stone or adhesions; peritonitis many times follows such obstructions; some of the neglected cases of stone are sure to become cancerous. An added complication is that of disease of the pancreas. If abscess of perforation occurs and the patient survives, the adhesions following causes much distress from dypepsia, and many times mechanically obstruct the outflow of the bile. Perforations from stones or abscess may form fistulous tracts into the abdominal organs or lung. External openings discharging stones are on record. Intestinal obstruction from large stone ulcerated into the bowel are of frequent occurrence.

The removal of gall-stones when they are all still confined to the gall-bladder is in the hands of competent surgeons now so safe from an operative standpoint, and so satisfactory in the relief of symptoms when early operation is performed, that in all cases a diagnosis of infection or stones within the bile passages should mean early operation. If we would only appreciate the serious end results that follow continued infection, inflammation, gall-stones, colics, and attacks of obstructive jaundice, there would be less pepsin sold for "dyspepsia," so-called, and fewer attempts at lubrications and dissolutions by the ingestion of "Italian olive oils," sal hepatica and natural waters (guaranteed to dissolve stone). Certain it is that they will not affect the condition. The temporary improvement sometimes noted under such treatment is due to the natural resistance of the tissues.

The surgery of the bile passages should not be the surgery of the end results of infection, nor of the complications, rather we should early attack the infected gall-bladder (as surgeons now do the appendix), drain the gall-bladder early, relieve the infection, thereby obviating the complications which give such unsatisfactory results. Medical efforts at drainage through the ducts usually fail. I would here like to cite some of my unsatisfactory cases, unsatisfactory because of delay in coming to operation. Surgical skill will not and can not recompense for delays. In the hands of a com-

petent surgeon, the early drainage cases should all do well. The most skillful surgeon can not relieve many of the complications that arise from delay.

Case I.—Mrs. H., aged seventy, blind for thirty years (cataracts) ; seen early in the fall of 1909; she was having severe cramps in the epigastrium. She gave a long history of dyspepsia, eructations, bloating, colics and constipation. Her abdomen was tender to the right of the middle line, a tumor about the size of an egg was felt under the edge of the ribs and down deep into the right hypochondrium. There was no jaundice and no enlargement of the liver. A diagnosis of cancer of the bile duct was made. In October, 1909, she developed obstructive symptoms, jaundice became marked and the liver greatly enlarged. About the end of October, 1909, the post-mortem was made, there was primary carcinoma of the common duct. In the center of the growth was a large stone lodged in the duct. There were numerous smaller stones packed in the liver ducts and in the gall-bladder.

Case II.—Mrs. M., aged forty-four, seen May, 1909. She gave a long history of stomach trouble with repeated attacks of vomiting, biliousness, distention, colics, and during the past year was jaundiced on several occasions. Examination revealed tenderness over the liver and gall-bladder regions. A tumor mass was felt near to the head of the pancreas. A diagnosis of carcinoma of the bile ducts and head of the pancreas. No operation was attempted. July, 1909, post-mortem showed primary malignant disease in the common duct and at the head of the pancreas. There were secondary deposits in the liver. Stones were present in the common duct.

Case III.—Mrs. F., aged twenty, seen April 27, 1911. Three days previous she was taken with a sudden and severe pain in the epigastrium, violent vomiting ensued, the vomitus containing bile and blood. Vomiting and pain were temporarily relieved by repeated hypodermics of morphia. Previously she had three such attacks and recovered, except between them a fulness within the abdomen and stomach trouble persisted.

Examination: The upper adbominal muscles were very rigid, the liver dullness merged with a dullness of a mass which extended downward and inward towards the umbilicus. Her temperature was 100° F., pulse 90; vomiting was again becoming a prominent feature. This was the fourth day from onset. There was no jaundice. A diagnosis of perforated duodenal ulcer or gall-bladder was made and patient sent to hospital for an immediate operation. At operation there was found perforated and gangrenous gall-bladder. The mass was omentum and pus. There were no stones. The patient recovered after a very long and stormy convalescence. Her present condition is far from satisfactory because of adhesions about the pylorus and duodenum.

Case IV.—Geo. L., aged fifty-six, first examination August, 1906, diagnosis was then made of gall-stones. Operation was advised but refused. Again seen during an attack in December, 1907, and in January, 1908, also

September, 1909, and September, 1911, and again in August, 1912. He was the son-in-law of a physician. The doctor was not convinced that he had gall-stones, but rather believed he had "duodenal catarrh." The present attack of August, 1912, was ushered in by severe chills, high temperature, vomiting and jaundice. Diagnosis by his physician at this time was malaria. His symptoms grew worse and on the third day an enormous mass was found in the right side. I was then called and diagnosed obstruction from gall-stones. He was removed to the hospital and an immediate operation performed. The gall-bladder contained one and a half pint of pus and bile, together with hundreds of stones. The cystic duct was obstructed by stone. A further examination failed to discover stones in the common or liver ducts. Drainage tubes were then placed in the gall-bladder and in the fossa under the gall bladder. His recovery was prompt but unsatisfactory. He has had no return of colic or vomiting, but has a sense of uneasiness and stomach distress due to pylorus and duodenal adhesions. His gall-bladder was drained for a period of six weeks.

Case V.—Miss M. D., age thirty-seven, October, 1911. Onset of present illness was with severe and sudden pain in the right side accompanied by vomiting, jaundice, chills and fever. When I saw her she had been ill for five weeks, she had a large and tender gall-bladder, was deeply jaundiced; she said she had lost weight. Her past history was that of colics and dyspepsia, such attacks extending over a period of thirteen years. Operation revealed many stones packed into the common duct. The gall-bladder was also filled with stones. The head of the pancreas was enlarged. Recovery from operation was prompt, all of the symptoms disappearing, and within three or four months she had gained twenty pounds. Six months later she had a recurrence of jaundice, chills, fever and vomiting. The jaundice was persistent. Being unable to determine whether stone or malignancy existed, I again explored the regions of the pancreas and gall-bladder. The head of the pancreas was much enlarged and obstructing the common duct. No stones were present. Malignancy was now certain. Nothing could be done. The patient failed to recover from the second operation, died on the third day following.

Case VI.—Mrs. L., aged forty-two. She had had years of stomach distress, gall-stones, colic and dyspepsia. For the past eight years she had taken morphia for the relief of pain. In January, 1913, she decided that she would be operated upon. Examination showed an enlarged and tender gall-bladder, the tenderness extending toward the mid-line and into the region of the pylorus. Exploration was done under intravenous hedonal anesthesia. Malignancy of the duct was certain. No attempt was made to remove stones that were present. She is still alive; there is at the present time an extension of the growth into the liver. Three to five grains of morphia are required daily for her relief. Her existence is miserable.

I could add other cases to the above list, but the few herein reported will suffice to make my point, that stasis of the bile within the bile passages, infections, gall-stones and chronic pancreatitis are the forerunners of cancers of the organs. When cancer does not develop chronic invalidism or morphinism many times occur. Abscess and perforation are other of the complications. Diabetes of hepatic origin or, rather, diabetes following infections in the liver and ducts is not so uncommon. I have observed two cases of diabetes developing after gall-stones, in women who previously had had no sugar in their urine. Both of these cases refused operation. The infection in these two cases was of long standing. Five or six years of recurring infection, jaundice and colics.

These cases were taken from a series of operations upon the gall-bladder and bile ducts done within the past five years. In Cases I and II of this report no operation was attempted. The cases were evident cancer at the time of my first examination. Case III shows the evil result of persistent infection causing perforation of the gall-bladder. There were no stones in this case, obstruction was caused by adhesions. Bacterial invasion of the mucosa and submocasa caused obstruction and perforation. The blood vomited in Case III may have come from a duodenal ulcer, mucous erosion occurring because of the infected bile flowing into the duodenum. Cases I, II, V and VI were cases of cancer developing from the chronic irritation of stone lodged in the ducts. In the cases operated, Case V had a history of gall-bladder infection and stone extending over a period of nearly thirteen years. Case VI had taken morphine for the relief of gall-stone colic for eight years. Such conditions should not be allowed to persist. Patients should be advised of the complications likely to arise. Operations performed early will obviate such complications, and it is the duty of the physician to warn the patient of the danger.

At the close of a clinical lecture delivered at the Infirmary, New Castle-on-Tyne (British Medical Journal, January 3, 1914), Mr. Rutherford Morrison said: "Lives are still lost that could be saved and a delay not so dangerous often means prolonged convalescence and a dangerous illness which might have been averted by more accurate diagnosis and more prompt action. Improvement has been most marked in the more tragic conditions, such as some perforating gastric and duodenal ulcers, because symptoms are so serious and so pronounced that everyone concerned is convinced that something should be done without unnecessary delay. There are still too many appendix cases left to form abscess or to develop peritonitis before operation, and still more gall-stones left till serious complications such as abscess, common duct obstruction and cancer render operations serious and unsatisfactory."

My plea then is to drain the gall-bladder early in infections. When gall-stone colic occurs there can be no permanent relief except that offered by operation. If ulcer of the duodenum is, as Monyhan and others believe it to be, due to infection, is it not reasonable to suppose that an infected bile

continually pouring into the intestinal tract would add to the chances of ulcer in the duodenum? Cancer arising from chronic irritation is admitted by many observers. A stone lodged in the gall-bladder or ducts—more particularly the ducts—is potentially a cause of cancer of those organs. Diabetes of hepatic organs, pancreatitis and some of the abscesses of the pancreas can be prevented by the early drainage of an infected bile.

THE INFLUENCE OF BILE ON THE FAT-SPLITTING PROPERTIES OF PANCREATIC JUICE.*

By B. K. Rachford, M. D.

Cincinnati.

Plate I.

In the spring and sumer of last year, in the Berlin Physiological Laboratory, I made a study of the fat-splitting properties of pancreatic juice and read a paper on this subject before the physiological section of the Tenth International Medical Congress. The complete and more detailed presentation of this work is the object of this paper.

The short paper on emulsion, apart from any interest or value that may attach to this portion of the paper itself, is of importance because of its bearing on the methods used in the study of pancreatic juice.

EMULSIONS

In 1870 E. v. Brucke[1] announced the fact that when rancid oil[2] is shaken with a solution of sodium carbonate and certain other alkaline fluids an immediate emulsion results. He believed that the oil was broken into fine globules by the shaking and that the soap formed served to hold the emulsion by preventing the union of the oil globules.

In 1878 Johannes Gad[3] called attention to the fact that when oil containing the proper percentage of fatty acid was placed on the surface of a carbonate of sodium solution a beautiful spontaneous emulsion resulted, and from this he held that neither shaking nor any other outside mechanical force was necessary to the formation of an emulsion, but that the chemical force developed by the soap formation was of itself sufficient under favorable circumstances to break the oil drops into the finest emulsion globules. There is but little room for doubt, I think, that Gad is right in his opinion. In fact, the only question which might arise is whether the force developed by the soap formation is not a physical (Quincke) rather than a chemical one. Gad also believed with Brucke that the soap formed had much to do with holding the emulsion, and this proposition is, I think, now everywhere accepted, although opinions differ widely as to the manner in which the soap acts in bringing about this result.

I wish here to call attention to the method used by Gad in his study of spontaneous emulsion, since this method is the basis of the methods used by me in the study of the fat-splitting properties of pancreatic juice.

A ¼% carbonate of sodium solution is placed in a series of watch-glasses, and drops of oil containing different percentages of fatty acid are gently placed, by means of a pipette, on the surface of the fluid in the watch-

glasses. The amount of spontaneous emulsion in the various glasses is carefully noted and compared, and in this way one can readily ascertain the percentage of fatty acid required to give the best emulsion.

It must, of course, be remembered in this connection, that the percentage of fatty acid required to give the maximum amount of spontaneous emulsion will vary with other conditions: such as temperature, strength of soda solution, etc., and that therefore only experiments made under similar conditions can be compared. By this method Gad observed that under otherwise similar conditions a certain definite percentage of fatty acid must be present in oil to give the maximum amount of spontaneous emulsion. For example, he found that with a ¼% carbonate of sodium solution at room temperature, about 5½% of fatty acid was required, and that with increasing or diminishing per cents. of acid above or below 5½ per cent. he got less and less emulsion, until finally there was no emulsion at all. A very little more or less than 5½ per cent. of acid gave an incomplete emulsion. He found, therefore, that the limits of good spontaneous emulsibility were not only constant but also quite narrow, and upon these important facts depends the value of his method.

We have in Gad's method a simple and accurate means of determining the proper percentage of fatty acids for giving the best spontaneous emulsion of any given oil under given conditions.

After repeating the experiments of Gad and confirming his observations I devoted considerable time to the study of the influence of shaking and other outside mechanical means on the formation of emulsions.

The oil used almost exclusively in my experiments was olive oil that had been neutralized by shaking for two hours with a saturated solution of barium hydrate at a temperature of 95° C. and then pipetted and filtered. Oil freshly prepared in this manner will be found practically neutral, and the term neutral olive oil as used in this paper always refers to such oil.

The stirring was done chiefly by currents of air carried from a blowing machine, into the liquids to be stirred by means of rubber tubing and glass rods. This method is not only more convenient but it has other advantages over the ordinary one of shaking the tube.

My experiments led me to the following conclusions:—

1st. No amount of stirring will give a permanent emulsion of either neutral olive oil or of rancid olive oil in distilled water. (Frey[4] found differently.)

2nd. No amount of stirring will give a permanent emulsion with neutral olive oil and a ¼% carbonate of sodium solution.

3d. Shaking rancid oil and a ¼% carbonate of sodium solution gives a good permanent emulsion, even though the oil contain a very small or a very large percentage of fatty acid.

From the above observations we see that when the conditions for soap formation are present, shaking very much widens the range of good emul-

sibility and promotes the formation of a good permanent emulsion, but when the conditions for soap formation are not present, the shaking has no influence whatever.

In our study of emulsions we must remember that two things are necessary to the formation of a good permanent emulsion.

1st. The oil must be broken into very fine globules.

2nd. These globules must not only be prevented from running together, but they must also remain rather uniformly distributed throughout the liquid. Now since we know that soap and certain other materials, as albumen and mucilage, have the power of holding emulsions, it would seem an easy matter to make a mechanical emulsion by shaking neutral oil in a solution of soap, albumen or mucilage; but such in truth is not the case. In my experiments with soap solution and neutral olive oil I found that in very heavy solutions of soap, by violent and prolonged stirring, I could get only an imperfect emulsion, one in which the oil globules were larger and more variable in size than those formed by spontaneous emulsion.

These mechanical emulsions do not approach in perfection a physiological emulsion, such as milk; and they can be formed only in very viscous liquids and with such great mechanical force as to place them beyond the pale of physiological importance.

For the study, therefore, of the influence of stirring in the formation of good permanent emulsions, such as may have some physiological importance, we must return to the experiments already noted, where a moderate amount of stirring very much hastened and promoted the formation of good emulsions when the conditions for soap formation were present.

The influence of stirring under such circumstances may, I think, be explained as follows. When too little acid is present for the formation of a good spontaneous emulsion, the shaking or stirring simply favours the emulsion by promoting soap formation. It breaks the oil into a number of small globules which are constantly presenting new surfaces to the surrounding alkaline fluid, thus enabling the soda to combine with all the fatty acid present, in the formation of soap, and the chemical force thus liberated by the soap formation becomes an important factor in the breaking of the oil drops into the fine emulsion globules, just as it does in pure spontaneous emulsion.

When too much acid is present for good spontaneous emulsion, the process is brought to a stand-still by the formation of a heavy soap membrane between the oil drop and the alkaline fluid, thus preventing further soap formation. Under these conditions, shaking breaks the oil drop and consequently the soap membrane, thus constantly presenting new surfaces of oil to the surrounding alkaline fluid and in that way favouring soap formation and the resulting emulsification. We see, therefore, that while shaking may play a very important role in the formation of emulsions, its action is chiefly an indirect one, promoting emulsification by favouring soap formation, and that the chemical force liberated by this process is the force most active in breaking the oil drops into fine emulsion globules. From my experi-

ments I formulate the following general law concerning the influence of stirring in the formation of emulsions.

The amount of stirring required to give a good emulsion of oil in a ¼ % carbonate of sodium solution will be in inverse proportion to the nearness with which the percentage of fatty acid in the oil approaches the proper percentage for giving the maximum amount of spontaneous emulsion. If the oil contains the exact percentage of fatty acid for giving the best spontaneous emulsion, then the shaking will be superfluous, since a good emulsion will form without motion and no amount of shaking can improve it. If, on the other hand, the oil be entirely free from fatty acid, then, as we have seen, no amount of shaking will give a good emulsion. Between these two extremes the above law applies, and shaking may contribute very largely to the formation of emulsions.

In the application of the above principles we have a simple and convenient method of determining when an oil is practically free from fatty acid; viz., shake it with a ¼ % solution of carbonate of sodium, and if there be no fatty acid present, the mixture rapidly clears.

By the same method we may tell when we have fatty acid free from admixture with oil; viz., shake the fatty acid with the soda solution, and if oil be present we will have more or less milky whiteness, which is characteristic of emulsions; but if no oil be present, we will have a simple cloudiness due to the insoluble soap formed. From all that has been said, it follows as a logical conclusion that the energy required to make an oil emulsible will be in direct proportion to the stability of the oil molecule of the given oil. The more stable the oil molecule, the more energy required to split it into fatty acid and glycerine. It matters not whether the energy be in the form of heat or of organized ferments, bacteria, or of unorganized ferments as the fat-splitting ferment of the pancreas.

During my experiments I found that heating neutral olive oil developed fatty acid and made it emulsible, and that if this heated oil be again neutralized it became non-emulsible, thus showing the emulsibility to be due to the acidity. I also found that the greater the heat and the longer applied, the more fatty acid was developed, so that boiled olive oil contained too much acid for good spontaneous emulsibility.

It is an interesting fact that the acids freed by heating various oils seemed to have greater power in making them emulsible than a like quantity of oleic acid. This is especially true of castor oil. Castor oil is not made more emulsible by the addition of oleic acid, but after boiling, it may be emulsified by shaking it with sodium solution, but it never becomes spontaneously emulsible; this latter fact Gad called attention to and thought it due to the viscosity of this oil. The stability of the castor oil molecule is shown by the great heat required to develop sufficient fatty acid to give an emulsion. These facts seem to indicate that the fatty acids of an oil are the fatty acids best adapted for giving emulsibility to this particular oil.

It is a physiological fact beyond dispute that the splitting of fats is a most important preliminary step in fat digestion. That the cooking of fats will develop in them fatty acid is therefore a fact of considerable physiological importance and one that, so far as I know, has not previously been noticed.

As I have previously intimated, it is my belief that the chemical force developed by soap formation is the chief factor in the formation of all physiological emulsions, that it plays quite as important a role in the formation of the emulsion as the soap does in holding it after it is formed.

That soap has the property of holding emulsions is, I think, an undisputed fact, but the manner in which the soap acts is a question concerning which there has been much difference of opinion. In explanation of this difficult problem I wish modestly to express my belief in a theory of emulsions which is a modification of that offered by Gad. Gad believed that the fine globules of oil were coated as soon as formed, with insoluble soap particles which formed a protecting envelope that prevented the oil drops from running together. The modification which I offer is as follows: the chemical process of soap formation which breaks the oil into fine globules must develop considerable heat, this must necessarily have the effect of bringing a certain amount of otherwise insoluble soap into solution. This heat will necessarily be local and felt chiefly just at the point where the soap is formed, and all the surrounding liquid will be cooler. The soap therefore which is brought into solution by the heat either is precipitated a moment later on coming in contact with cooler parts of the liquid, or it causes increased viscosity in the liquid.

We may, therefore, say that the heat is developed, the soap formed and dissolved and the oil broken by the same force in the same place and at the same time. By this mechanism the oil globules are, as soon as formed, coated with a liquid soap which a moment later hardens about them in the form of soap membranes. These soap membranes at the moment of their formation are not as capable of holding the globules as they are later, when, on cooling, they become more resisting. If this theory be true, it would follow that an appreciable length of time must elapse after the formation of an emulsion before it reaches its highest degree of stability. And this in fact I find to be true, that the emulsions can be more easily destroyed at the moment of their formation than later, and it is only in explanation of this and other facts that the above theory is offered. The following conclusions I draw from my experiments, and some of them are best explained by this theory.

1st. If bile be present an emulsion cannot form, although all the conditions otherwise favourable to its formation be present. This fact was pointed out by Gad, and he offered in explanation that the soap-dissolving properties of the bile prevented the formation of insoluble soap membranes, and that the unprotected oil globules ran together and came to the surface as free oil.

2nd. If bile is added to an emulsion, the moment after it is formed the emulsion rapidly clears by creaming, but no free oil appears on the surface. Here it seems that the soap not in membranes is dissolved. This increases the specific gravity and diminishes the viscosity of the liquid, and as a result the soap-coated globules rise to the surface as cream; why it is that the soap in the membranes more quickly acquires the property of resisting the solvent action of bile than the soap not in membranes I cannot say, yet this seems the only explanation of the above phenomenon.

3rd. If bile be added to an emulsion some minutes after it has formed, it has no effect in destroying the emulsion. The above propositions clearly indicate that an appreciable length of time must elapse after the formation of an emulsion before it reaches its highest degree of stability.

4th. One-tenth per cent. nitric and sulphuric acid and one-fifth per cent. lactic acid solutions rapidly destroy emulsions, the free oil running to the surface. Acids destroy emulsions by combining with the base of soaps and freeing the fatty acids; the soap being thus destroyed, the liquid is much less viscous while the specific gravity is very little altered. The oil globules are therefore driven to the surface as cream, but if the acid be stronger, the soap in membrane is also destroyed, and free oil floats on the surface. The membrane soap is here found to be more resisting to soap destroyers than soap not in membranes.

5th. Hydrochloric acid has a much less destructive influence on emulsions than has nitric or sulphric acid, and lactic acid has a less destructive influence than acetic.

6th. If sapo medicatus[5] be shaken in a $\frac{1}{10}\%$ nitric or sulphuric acid solution the soda of the soap will combine with the nitric or sulphuric acid and fine globules of free fatty acid will rise to the surface. Sapo medicatus is more easily destroyed by nitric and sulphuric acids than it is by hydrochloric acid. These facts strongly corroborate the opinion that acids destroy emulsions by destroying soaps.

THE FAT-SPLITTING PROPERTIES OF PANCREATIC JUICE

Since the publication[6] of Claude Bernard, physiologists have generally believed that pancreatic juice has the property of splitting neutral fats into fatty acids and glycerine. Claude Bernard himself believed that the pancreatic juice had a two-fold action on fats. In the first place, he said that when neutral oil and pancreatic juice were shaken together an instantaeous emulsion resulted. In the second place, that the prolonged action of pancreatic juice on neutral oil would develop fatty acid. He did not in any way associate these two processes and believed them to be due to entirely different properties of the juice, the emulsion being an instantaneous process and the fat splitting occurring only after considerable time. And these two processes are still described as separate and distinct properties of pancreatic

[5] A soda-soap made with olive oil acids.
[6] Compt. rend. de l'acad. de Paris, T. xxxiii. Arch. général, 1849. Memoire sur le Pancreas, Paris, 1856.

juice in some of our most recent text-books. But since the publications of Brucke and Gad, most German physiologists have associated these processes, believing that the emulsion was wholly due to the fatty acid which had been developed in the oil by the fat-splitting ferment and that the matter of inference from the works of Brucke, Gad and others, rather than from actual experiments with the juice itself. I have failed to find that any systematic work in this direction had been done with pancreatic juice since the days of Claude Bernard. Quite a number of attempts have been made, but the difficulties in obtaining a normal juice were so great that no extensive work has been done and no important fact added to our knowledge. But while almost no work has been done with the juice itself, an immense amount of work has been done with pancreatic extracts and infusions made from the gland. Physiologists have seemed to take for granted that, in studying the physiological properties of pancreatic juice, the juice itself offered no advantage over these extracts. In fact they seemed to believe from the great difficulty in obtaining a normal juice that the extracts were preferable, and our knowledge of the present day is based almost exclusively on experiments with the extracts, and but for the fact that they contain a fat-splitting ferment the time-honoured opinion of Claude Bernard would have carried but little weight. For these reasons, a systematic investigation into the fat-splitting properties of the pancreatic juice seemed to offer a fertile field for work.

Although in the beginning the obstacle of obtaining normal juice in sufficient quantities to prosecute this investigation seemed insurmountable, yet I was fortunate enough to hit upon a method by which I could readily obtain from the rabbit a normal juice in sufficient quantities for experimental purposes. The operation for temporary pancreatic fistula in the rabbit is easily and quickly done as follows: Make an abdominal incision in the linea alba two and one half inches long. Bring the duodenum, which is readily found high up in the right hypochondriac region, through this opening, run down the gut to a point where the peritoneum binds it so closely that it will not come through the opening, and just at this point will be found the pancreatic duct as it runs through a leaf of the pancreas to the small intestine. Resect two inches of the intestine at this point, leaving its mesenteric attachment, tie the cut ends of the intestine above and below and drop them in the cavity, bringing the resected portion through the abdominal wound. The abdominal wound is now partially closed by stitches, leaving only sufficient opening for the mesentery running to the resected gut. This resected gut is now laid open opposite the mesenteric attachment and spread out on the abdominal wall. The ends of the gut are clamped and its margins packed with absorbent cotton to prevent bleeding. Insert a small glass canula through the pancreatic papilla into the pancreatic duct and cover the exposed mucous membrane with absorbent cotton saturated with common salt solution. The flow of juice begins at once and continues from four to six hours. In this manner about 1 cc. of juice uniform and powerful in

physiological action may be collected. This operation is a modification of the Heindenhain permanent fistula operation[7] and has the advantage of being simple and uniformly successful.

In my experiments I used the pancreatic juice of the rabbit, as it seemed quite impossible for me to obtain from the dog a normal juice in sufficient quantities for experimentation. The fat used was neutral olive oil.

I worked for several weeks with very faulty methods before I hit upon the method which I afterwards used and which, I think, is admirably adapted to the study of the fat-splitting properties of pancreatic juice. The foundation-stone of the method is the spontaneous emulsion method of Gad. We have previously seen how by this method we may determine when an oil has the proper percentage of fatty acid to give the best spontaneous emulsion under certain given conditions. After having established the conditions under which one can get a good emulsion with a certain per cent ($5\frac{1}{2}$) of fatty acid, it is evident that we can use this method for determining when an oil has this percentage of fatty acid, and since the completeness of the spontaneous emulsion will be in direct proportion to the nearness with which the quantity of fatty acid in the oil approaches this percentage, we have also a method of estimating the amount of increase of fatty acid in any oil by testing its spontaneous emulsibility from time to time. For example, let us suppose that we have a neutral oil in which fatty acid begins to develop, and that this process slowly continues until all the oil is changed into fatty acid and glycerine. If the test of spontaneous emulsibility be applied to such an oil by placing a drop of it from time to time on carbonate of sodium solution, we get at first no emulsion at all, and then with the development of some fatty acid a slight emulsion, then more and more with increasing quantities of acid until the maximum emulsion is reached, which indicates that about five and a half per cent. of acid has been developed. The emulsion then decreases with the further increase of acid until finally we get no spontaneous emulsion at all, which indicates about twelve per cent. of acid. Beyond this point the increase of acidity cannot be measured by spontaneous emulsion, but in this particular and under these circumstances the emulsion formed by shaking is of some value, for good emulsions may still be had in this way after too much acid has been developed for spontaneous emulsion. But the greater the amount of acid the more shaking is required to give a good emulsion, until finally when all the oil has been changed into fatty acid and glycerine we get no emulsion at all, but only a cloudiness due to the insoluble soap formed. In this method we have a simple means of approximately estimating the increase of fatty acid in an oil and of determining when all the oil has been changed to acid and glycerine. This method is not used to determine the exact quantity of acid which an oil contains, but is used rather to make a comparative estimate of the amount of acid in the same oil at different times and in different oils at the same time.

This method is applied to the study of the fat-splitting properties of pancreatic juice in the following manner. Arrange a series of watch-glasses containing a ¼ % solution of carbonate of sodium. Take a small test tube of 2 cc. capacity and place in it ⅓ cc. of pancreatic juice and twice as much neutral olive oil. Shake the tube and allow the juice and oil to separate, then pipette a drop of oil from the surface and place it on the soda solution in watch-glass I. Again, shake the tube and allow the oil and juice to separate, then pipette a drop of oil in watch-glass 2. Again shake and pipette as before, and repeat this process every three or four minutes until the experiment is completed. The beginning of the experiment and the time of each pipetting must be carefully noted. If the pipettings are three minutes apart, then the first drops of oil will have been exposed three minutes to the action of pancreatic juice, the second drop six minutes, the third drop nine minutes, and so on. By the amount of spontaneous emulsion occurring in these drops when placed on the soda solution one can comparatively estimate the quantity of fatty acid they contain. For example, in an experiment such as I have just narrated one may find very little emulsion in glass 1, more in 2, a fair emulsion in 3, good in 4, and the maximum in 5, and then the emulsion gradually decreases. By such experiments as this the fat-splitting properties of pancreatic juice can be beautifully demonstrated, and an idea formed of the rapidity of its action. There is a possible element of error in this method which had better be spoken of here. It would seem that the alkali of the pancreatic juice would combine with the fatty acids forming soap and in this way the oil would soon be emulsified in the juice itself and not separate after shaking. This would indeed be a serious drawback if it actually occurred, but in truth it does not occur until late in the experiment after we have obtained the information we sought by the spontaneous emulsion method. It is true that after a large quantity of acid has developed and by repeated shaking we get an emulsion of oil in the juice which somewhat interferes with the method. Although the sodium in the pancreatic juice exists in the form of a carbonate, it seems to be peculiarly associated with some other substance which interferes with its combining with fatty acid in the formation of soaps. This may be illustrated by the following interesting experiment. Place in a small test tube drawn out like a pipette equal quantities of pancreatic juice and neutral olive oil, ½ cc. each. Shake the tube and set aside for twenty-four hours. At the expiration of this time break the pipette point and allow the contents of the tube to escape slowly through the opening thus formed in the bottom of the tube. The pancreatic juice, being at the bottom, is the first to escape, and it is clear and strongly alkaline; then comes the oil which formed the upper layer, and it is strongly acid. Here we have a rancid oil and an alkaline fluid in contact for twenty-four hours with very little soap formation. This experiment clearly indicates that something interferes with the formation of soap from the alkalies of the pancreatic juice. This is a plausible explanation of why the element of error caused by soap formation does

not interfere with the practical application of the method. But even the small element of error which is introduced by soap formation may be reduced to a minimum by using small quantities of juice and three or four times as much oil, and in that way the quantity of soda is greatly reduced and the action of the juice is but slightly retarded. This latter seems a strange statement, yet I have found in my experiments that within the limits named, the same quantity of juice splits large quantities of oil almost as readily as small. In passing, let me again call attention to the experiment above narrated as a simple and striking lecture experiment. The alkalinity of the juice and the acidity of the oil as it follows through the same opening may be demonstrated by litmus paper or solution. With these details as to method we are prepared to consider pancreatic juice and its action on neutral fats.

1st. The pancreatic juice of the rabbit is alkaline and remains so for some time after it is removed. On two occasions I tested juice that had stood exposed at room temperature for twenty-four hours and found it alkaline and physiologically active. Different specimens of pancreatic juice may vary in physiological activity. As a rule, the juice obtained from a fistula that has been acting several hours is not as active as juice from the same fistula obtained soon after the operation.

2nd. If pancreatic juice be shaken with neutral olive oil, the oil rapidly takes on an acid reaction. That this acidity is due to fatty acid is shown by the facts that all the acid may be extracted with ether and the oil made emulsible by its presence. The gradual yet rapid development of fatty acid by the action of pancreatic juice on neutral olive oil may be beautifully demonstrated by pipetting drops of oil at intervals from the surface of a mixture of pancreatic juice and neutral olive oil and placing them on a $\frac{1}{4}\%$ solution of carbonate of sodium in a series of watch-glasses. Soon we have a slight emulsion, then more and more until the maximum is reached, then the amount of emulsion becomes less and less as too much fatty acid is developed, until finally we have no spontaneous emulsion at all. That an excess of fatty acid is the cause of the decrease and cessation of spontaneous emulsion may be demonstrated as follows. Take a drop of oil from a mixture of oil and pancreatic juice after it has passed the limits of spontaneous emulsibility and mix it with neutral olive oil, and the mixture is spontaneously emulsible. In one experiment, for example, I took one drop of oil that had passed the stage of spontaneous emulsibility and mixed it with four drops of a neutral olive oil, and one drop of the mixture on soda solution gave a beautiful spontaneous emulsion. Here one drop of the oil acted on by the juice contained sufficient fatty acid to make five drops of oil spontaneously emulsible, that is, to give five drops of oil about $5\frac{1}{2}\%$ of fatty acid. The drop of oil acted on by the juice must therefore have contained about 30% of fatty acid and the time required to develop it was thirty-five minutes. Since 30% of acid is so quickly developed, it seems

a fair inference that the prolonged action of the juice would change all the oil fatty acid and glycerine, and such in fact is found to be the case.

3rd. All the oil is split into fatty acid and glycerine by from one to two hours' action of the pancreatic juice—time varies with the specimen of the juice. This may be shown by pipetting such fatty matter from the surface of the juice and shaking it with soda solution and no emulsion will result, simply a little clouding such as occurs when fatty acid is shaken with soda solution. But if one drop of this same fatty matter be mixed with six or eight drops of neutral olive oil, this mixture will, on being shaken with soda solution, give a good emulsion. This experiment is best performed by adding a small quantity of bile to the juice before adding the oil. The bile does not interfere with the fat-splitting action of the juice, but it does interfere with the formation of an emulsion, and for that reason the oil and juice continue to separate after shaking.

4th. The time required for pancreatic juice, acting in glass tubes at room temperature, to develop sufficient fatty acid ($5\frac{1}{2}\%$) in neutral olive oil to give the maximum spontaneous emulsion varies with different specimens of the juice and with the amount of shaking to which the juice and oil are subjected, but the average time as taken from my experiments was twenty minutes. In very active specimens of the juice it occurred as early as seven minutes, and in very poor specimens as late as sixty minutes. I also found that the juice did not act more rapidly in a basin of intestine than in the test tubes. In these experiments the resected intestine containing the pancreatic papilla was held by a fenestrated quadrilateral clamp made for the purpose, and into the basin of the intestine thus formed the pancreatic juice would ooze. Neutral olive oil was dropped into this basin and mixed with the pancreatic juice, and this oil did not become spontaneously emulsible more quickly than the oil in the test tubes, but the conditions here are also far from resembling those occurring in the normal duodenum, and the average rate of fat-splitting as established by these experiments is probably considerably below the rate at which fats are split in the duodenum. It is probable that the time required by the most active juice more nearly represents the rapidity of action of pancreatic juice in the duodenum.

5th. The action of pancreatic juice on most of the fats is rapid and complete.

Castor oil is a notable exception to this rule, as only a very small quantity of acid is developed in it by the action of pancreatic juice for five hours at $37°$ C. Castor oil is therefore practically indigestible and this may in part account for its cathartic action.

Pancreatic juice acts slowly on fats which have a melting point above body temperature, but it is an interesting physiological fact that their solidity at body temperature does not prevent their being split. Spermaceti for example, the melting point of which is above $38°$ C., is slowly split by the action of the pancreatic juice.

6th. As I have previously said, the pancreatic juice of the rabbit and neutral olive oil when shaken together show very slight tendency to the formation of an emulsion, and it is only after considerable acid has developed that repeated shaking will give a mixture resembling an imperfect emulsion. But if we mix and shake at intervals one part of neutral olive oil and one part of pancreatic juice for about fifteen minutes, and then add six parts of soda solution, we get at once an apparently good emulsion. This emulsion does not remain good; it always in the course of an hour or two clears by creaming, when the whole mixture will be found to have a strong acid reaction due to the large quantity of fatty acid developed. Whatever may be the explanation of the clearing of this pancreatic emulsion, the fact remains that an emulsion will form in the presence of pancreatic juice if carbonate of sodium solution be added, but it does not remain permanent.

7th. A permanent pancreatic emulsion may be formed by pipetting the oil from the surface of a tube containing oil and juice and shaking it with the carbonate of sodium solution. The emulsion formed in this way remains very much the same for an indefinite length of time. In this experiment the oil is made emulsible by the action of the juice and is then separated from it and emulsified with the soda solution; the emulsion itself contains no pancreatic juice and therefore does not clear. This permanent pancreatic emulsion reacts to emulsion destroying agents and soap dissolvers very like a fatty acid emulsion made with rancid oil and sodium solution. For example, it is not destroyed by the addition of bile or fatty acids, but is destroyed by mineral acids, resisting hydrochloric better than nitric and sulphuric acids. The pancreatic emulsion also resembles the simple rancid oil emulsion in that an appreciable length of time must elapse after its formation before it reaches its greatest degree of stability. This may be demonstrated by adding bile in excess immediately after the formation of the emulsion, when it destroys the emulsion by creaming, but if the bile be added later no such effect is produced. It also resembles the rancid oil emulsion in that it cannot form at all in the presence of bile.

The most important application of the method I have described is in obtaining comparative information concerning the fat-splitting properties of pancreatic juice. This application of the method may best be explained by detailing an experiment inquiring into the difference in the rapidity of action of pancreatic juice at room (18° C.) and at body temperature (37°).

Arrange two rows of watch-glasses containing a ¼% carbonate of sodium solution. Take two small test tubes, ⅓ c.c. of the same pancreatic juice in each, and to each tube add ⅓ c.c. of neutral olive oil. Shake both tubes equally and place one of them (A) in a sand bath kept in an oven at 37° C. and leave the other (B) at room temperature. At the expiration of three minutes pipette a drop of oil from A and place it in watch-glass 1, row 1; then as quickly as possible, with a clean pipette, take a drop from B and place it in watch-glass 1, row 2. Both tubes are shaken and replaced and at the expiration of three minutes a drop is again pipetted from the sur-

face of each. That from A is placed in row 1, that from B in row 2. This process is repeated again and again to the end of the experiment. At the close of the experiment it will be found that the emulsion occurs almost twice as quickly in row 1 as in row 2. The three-minute drop of oil from A gives as good an emulsion as the six-minute drop of oil from B, and the nine-minute drop of oil from A gives the same emulsion as the eighteen-minute drop of oil from B. Since these tubes were, apart from the temperature, treated as nearly alike as possible, we infer that pancreatic juice acts about twice as rapidly at 37° C. as it does at 18° C. The average ratio of increased rapidity of action, taken from my experiments, was as one to one and eight-tenths.

Whatever objections may be urged against the absolute accuracy of the figures obtained by this method, the same do not apply to the comparative accuracy of these figures. Even though we may not be able by this method to estimate the amount of acid produced by pancreatic juice in nine minutes acting at 37° C., we do know by this method, whatever this amount may be, that it requires one and eight-tenths times as long for pancreatic juice to produce the same amount at 18° C. In comparative experiments such as this it is not necessary nor practicable to have an equal length of time between the pipettings, but it is important that the tubes should be shaken at as nearly the same time and pipetted at as nearly the same time as possible, so that the oil drops to be compared by spontaneous emulsibility may have been exposed to the action of the juice for the same length of time, thus establishing the comparative accuracy of the results.

The great value and wide appliction of this method is seen in the study of the influence of bile and other agents on the fat-splitting action of pancreatic juice.

Bile alone does not split fats. This seems a well established physiological fact, which may be confirmed by shaking neutral olive oil and bile in a test-tube and pipetting the oil at intervals to the surface of a carbonate of sodium solution as in previous pancreatic experiments, when it will be found that oil shaken with bile for twenty-four hours does not become emulsible. The value of this method is here most conspicuous as the emulsibility of the oil could not be tested in the presence of the bile, because the bile would prevent an emulsion even if the fatty acid had been developed. But in this method the oil is separated from the bile after they have been in contact twenty-four hours and its emulsibility tested, and in this point lies the great value and wide application of the method, since the very agents, such as bile and hydrochloric acid, which have the greatest influence on the fat-splitting action of pancreatic juice, are the agents which interfere with the formation of emulsions.

Fresh rabbit bile removed from the gall bladder was used in all my experiments.

In every comparative experiment the pancreatic juice which had been collected in a single tube was divided into two, three or four equal parts

according to the number of tubes used in the experiment. The bile was also shaken and divided just previous to the experiment. In this way I could be reasonably sure that I was working with the same bile and same pancreatic juice in all the tubes.

By the methods described I reached the following conclusions.

1st. An equal amount of fresh rabbit's bile will, on being added to rabbit's pancreatic juice, greatly hasten its fat-splitting action in the ratio of three and one-fifth to one. In experiments of this kind, tube A contains $\frac{1}{3}$ cc. of pancreatic juice and $\frac{1}{2}$ cc. of neutral olive oil, and tube B contains $\frac{1}{3}$ cc. pancreatic juice and $\frac{1}{3}$ cc. bile and $\frac{2}{3}$ cc. of neutral olive oil. These tubes are treated alike and the emulsibility of the oil is tested from time to time as previously described. In this way the comparative rapidity with which fatty acid is developed in the oils may be determined. It is evident that in every experiment we can have two sets of figures from which to make our average, viz. the time required for the beginning and the time required for the maximum of spontaneous emulsion. In my general averages I have used both sets of figures, striking an average between them.

2nd. An equal quantity of a $\frac{1}{4}$% solution of hydrochloric acid will, on being added to pancreatic juice, retard its fat-splitting action in the ratio of two-thirds to one.

3rd. A mixture of equal quantities of bile and a $\frac{1}{4}$% hydrochloric acid solution will, on being added to pancreatic juice, greatly hasten its fat-splitting action in the ratio of four to one. The bile not only neutralizes the retarding influence of the hydrochloric acid on the fat-splitting properties of the juice, but it really acts more powerfully in hastening the action of the juice when in the presence of this acid than it does when acting alone. The contents of a series of tubes will best explain the class of experiments upon which this statement is based.

Tube A contains $\frac{1}{3}$ cc. pancreatic juice and $\frac{2}{3}$ cc. neutral olive oil. Tube B contains $\frac{1}{3}$ cc. of pancreatic juice, $\frac{1}{3}$ cc. of bile and $\frac{2}{3}$ cc. neutral olive oil. Tube C contains $\frac{1}{3}$ cc. of pancreatic juice, $\frac{1}{6}$ cc. of bile, $\frac{1}{6}$ cc. of a $\frac{1}{4}$% hydrochloric acid solution, and $\frac{2}{3}$ cc. of neutral olive oil.

Three rows of watch-glasses containing soda solution having been arranged for the reception of the oil drops, the tubes are now shaken and pipetted as in previous experiments and the time and the result are carefully noted. In row 1 containing the oil drop from A, the emulsion begins in eight minutes, and reaches the maximum in twenty minutes. In row 2 containing the oil from B, the emulsion begins in two and a half minutes and reaches the maximum in six and a quarter minutes. In row 3 containing the oil drop from C, the emulsion begins in two minutes and reaches the maximum in five minutes. These figures are the averages of a number of experiments.

4th. If an equal quantity of a 3% solution of glycocholate of soda be mixed with pancreatic juice it hastens the fat-splitting action of the juice in the ratio of two and one-fifth to one.

5th. A mixture of equal quantities of a 3% solution of glycocholate of soda and a ¼% solution of hydrochloric acid will, on being added in equal quantities to pancreatic juice, hasten its fat-splitting action in the ratio of two and one-third to one.

The glycocholate of soda solution, like the bile, not only neutralized the retarding influence of hydrochloric acid on the fat-splitting action of the juice, but it really acts more powerfully in hastening the action of the juice when in the presence of the acid than it does when acting alone. It must also be noted that the glycocholate of soda does not act as powerfully in hastening the fat-splitting action of the juice as the bile does. In the presence of bile the juice acts three and one-fifth times as rapidly as it does alone, and in the presence of a three per cent. solution of glycocholate of soda it acts two and a fifth times as rapidly. In the presence of bile and hydrochloric acid it acts four times as rapidly, and in the presence of glycocholate of soda and hydrochloric acid it acts two and four-fifths as rapidly. From this I infer that this property of the bile is chiefly but not wholly due to the glycocholate of soda it contains. The class of experiments by which these conclusions were reached is illustrated in Plate I, which is in part reproduced from a photograph.

6th. If one part of pancreatic juice be diluted with five parts of a ¼% carbonate of sodium solution its fat-splitting properties will be greatly retarded—in the ratio of one to eight—and further dilution with soda solution gives greater retardation, this property of the juice being practically destroyed when it is ten times diluted with this strength of soda solution. That this retarding influence is due to the soda, and not to the dilution, is shown by the fact that if pancreatic juice be diluted with five parts of distilled water, its fat-splitting action is very slightly, if at all, retarded.

The retarding influence of soda solution may be shown by the same kind of experiments used to show the influence of bile, hydrochloric acid etc. on the fat-splitting properties of pancreatic juice. But it seems possible that there might be considerable cause of error in this class of experiments, because of the presence of soda solution in one of the tubes. In an experiment of this kind, for example, one tube contains ⅓ cc. of pancreatic juice and ⅔ cc. of neutral olive oil, the other contains in addition to the same quantity of juice and oil ⅝ cc. of soda solution. In pipetting oil from the surface of two such tubes to test its spontaneous emulsibility, will not the result be greatly vitiated by the soda solution in one of the tubes, neutralizing the fatty acid as soon as formed? Theoretically this would seem to be an important source of error, but practically it is not of very great importance, since the results obtained by this method correspond closely to those obtained by another method which has not this source of error. The following experiment will illustrate this method. Take two small glass tubes. In one place ⅓ cc. of pancreatic juice and ⅓ cc. of neutral olive oil. Shake four or five minutes and add ⅝ c.c. of soda solution and an immediate emulsion will result. To the other tube add ⅓ cc. pancreatic juice and ⅓ cc. of neutral

olive oil and ⅝ cc. of soda solution. Shake, and the emulsion will not appear for thirty or thirty-five minutes. In the first tube, the pancreatic juice acting alone on the neutral oil produced enough acid in four or five minutes to make the oil emulsible on shaking it with the soda solution. But in the tube 2, the presence of the soda solution retarded the action of the juice so that it required thirty minutes to produce sufficient fatty acid to give an emulsion. Carbonate of soda solution therefore retards the fat-splitting action of pancreatic juice in the ratio above given.

In the accompanying diagram I have taken a line twenty millimetres long to represent the working power of pancreatic juice acting alone at room temperature. The other lines represent the comparative working power of pancreatic juice under the conditions named, and were obtained from averaging all my experiments.

DIAGRAM SHOWING THE INFLUENCE OF BILE AND OTHER AGENTS ON THE FAT-SPLITTING PROPERTIES OF PANCREATIC JUICE

Pancreatic juice at 18°C.
20 Mil. ━━━━━━ 1

Pancreatic juice at 37°C.
36 Mil. ━━━━━━━━━ 9,

Pancreatic juice at 18° C. and HCl.
13 Mil. ━━━━ ⅔

Pancreatic juice at 18° C. and glycocholate of soda.
44 Mil. ━━━━━━━━━━━ 1¹,

Pancreatic juice at 18° C. and glycocholate of soda and HCl.
56 Mil. ━━━━━━━━━━━━ 14,

Pancreatic juice at 18° C. and bile.
64 Mil. ━━━━━━━━━━━━━ 16,

Pancreatic juice at 18° C. and bile and HCl.
80 Mil. ━━━━━━━━━━━━━━━━ 4
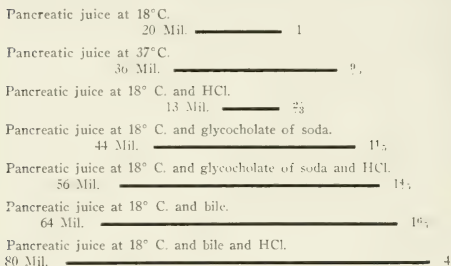
The above diagram and accompanying figures are offered as the clearest and briefest manner of expressing the difference in the rapidity of action of the various mixtures. It is not even hoped that these figures are absolutely correct, but it is my belief that relatively they are approximately correct, and therefore have an all important bearing on the pancreatic digestion of fats. We may summarize.

(1) Pancreatic juice can, acting alone, do a certain piece of work in x minutes, viz. develop in neutral olive oil a sufficient quantity of fatty acid to give the best spontaneous emulsion.

(2) Pancreatic juice acting in the presence of five parts of a ¼% carbonate of soda solution will require $8x$ minutes to do the same work, and in the presence of ten parts of the same solution its action will be almost destroyed.

(3) Pancreatic juice acting in the presence of an equal quantity of a $\frac{1}{4}\%$ solution of hydrochloric acid will require $\frac{3}{2}x$ minutes to do the same work.

(4) Pancreatic juice acting in the presence of an equal quantity of mixture of bile and a $\frac{1}{4}\%$ hydrochloric acid solution will require only $\frac{1}{4}x$ minutes to do the same work.

From the last two propositions it would follow that, if bile be added to pancreatic juice which is acting in the presence of hydrochloric acid, the fat-splitting action of the juice will be hastened as $\frac{3}{2}$ to $\frac{1}{4}$ or as six to one, and reversely, that if the bile be withdrawn or cut off from pancreatic juice which has previously been acting in the presence of both bile and hydrochloric acid, the fat-splitting properties of the juice will be retarded as six to one.

APPLICATION OF THESE PRINCIPLES TO THE INTESTINAL DIGESTION OF FATS

It is needless to say that my experiments were planned with the idea of placing pancreatic juice under conditions as nearly as possible resembling those under which it acts in the intestine. The influence of a $\frac{1}{4}\%$ solution of HCl was studied because of the presence of this acid in the duodenum where the pancreatic juice comes in contact with the fats. The influence of bile and of a mixture of bile and hydrochloric acid were studied for the same reason. The influence of dilution with a $\frac{1}{4}\%$ solution of carbonate of sodium was studied because it was thought, that, as the pancreatic juice passed downward into the small intestine, it might be subjected to some such influence, since the succus entericus contained this percentage of carbonate of soda. The conclusions therefore to which I have arrived must, if true, have a very important bearing in the explanation of the intestinal digestion of fats. I infer from my experiments that in the duodenum the mixture of bile tnd hydrochloric acid furnishes the best known conditions for expediting the fat-splitting action of pancreatic juice, and the cutting off of the bile would retard the fat-splitting action of the juice six times. It may also be of some physiological importance to note that the agents bile and HCl which expedite the fat-splitting absolutely preclude the formation of emulsions. The duodenum therefore offers the most favourable conditions for the splitting of the fats and the most unfavourable for their emulsification. In the jejunum and ileum these conditions seem to be exactly reversed. The intestinal juice containing, as it does $\frac{1}{4}\%$ of carbonate of soda, would not only furnish the conditions for the spontaneous emulsification of the rancid fats, but would also retard the fat-splitting action of the pancreatic juice. I do not wish to express the belief that intestinal juice plays just such a role as this in the intestinal digestions of fats, but only offer it as a deduction from test tube experiments, thinking it may have some physiological bearing.

From my experiments I infer that pancreatic juice must act very rapidly under the favourable conditions found in the duodenum. In some of my experiments at room temperature, good specimens of pancreatic juice aided by the presence of bile and hydrochloric acid produced, in neutral olive oil, $5\frac{1}{2}\%$ of fatty acid in two minutes. At body temperature this work would have been accomplished in one minute, and under the favourable conditions offered by the duodenum it would probably have been done in even less time.

This rapidity of action of pancreatic juice is of great physiological importance since it is evident that at this rate, all the fats would be split into fatty acid and glycerine in the time required for intestinal digestion, unless this action of the juice was checked or retarded in some manner.

IMPORTANCE OF BILE IN THE INTESTINAL DIGESTION OF FATS

The various conditions which have an influence on the intestinal digestion of fats have been developed by natural selection, and so far as we know they are the best for the purposes they serve. The comparative immobility of the duodenum, its close attachment to the head of the pancreas, its horse-shoe shape, all, no doubt, have an influence on the rate of passage of food stuffs. This rate, which is chiefly controlled by these and other anatomical conditions, was established to accord with normal digestive functions, and by this mechanism the fats are exposed to the action of pancreatic juice just long enough to allow for whatever action that juice may have in fat digestion. Let us suppose that under normal conditions the fats are exposed in the duodenum to the action of pancreatic juice for x minutes, and that this time is just sufficient to allow for whatever fat-splitting is necessary at this point. Now if the bile be cut off, the rate of passage of the food stuffs, which is chiefly controlled by anatomical conditions, remaining the same, the fat would still be exposed to the action of the juice for only x minutes. But since in the absence of the bile the pancreatic juice is able to accomplish only $\frac{1}{6}$ of the fat splitting which it normally does it would follow that the fats would pass with only $\frac{1}{6}$ of the amount of splitting that normally occurs, and since the splitting of the fat is, as recognized by all physiologists, a necessary preliminary step in fat digestion, it would follow that the fats would pass in great part undigested. This gives to bile a most important and definite position among the juices which assist in fat digestion, since we have here pointed out at least one of the ways in which it exerts its wonderful influence in fat digestion. Physiologists have been led to believe through much clinical and experimental[a] evidence that the bile was necessary to fat digestion. How and where it acted has been one of the greatest of physiological mysteries. The experiments of Westinghausen[a] seemed to show that bile promoted the passage of the fats through membranes, and this was thought by some physiologists to have a bearing on the absorption of fats.

But since the publication of Groeper[10] denying that bile had any such action we have been quite as much at sea as ever in explaining the action of bile in fat digestion.

I wish to thank Prof. Gad for his kindness and advice during the prosecution of these studies.

10. Archiv. für Anat. u. Phys., 1889.

ADHERENT HERNIAS OF THE LARGE INTESTINE.*

By J. Louis Ransohoff, M. D.

Cincinnati.

Sliding hernia of the sigmoid is a subject which as a rule does not receive the attention it merits. In most text-books on surgery, even in some of the treatises on hernia, it is barely mentioned. Though uncommon, it is one of the most important forms of hernia, its importance lying in its recognition during operation. If unrecognized, proper operative steps cannot be instituted, and the viability of the bowel may be jeopardized.

Since the first accurate description by Scarpa in 1812, it has been variously known as adherent hernia of the large intestine, hernia with incomplete sac or sliding hernia, the *hernie par glissmente* of French authors. As I hope to show, the only proper designation is adherent hernia of the large intestine, the other terms being misnomers, based on faulty conception of pathogenesis.

The most widely accepted theory is that this form of hernia occurs by the sliding of the gut on the posterior peritoneum. Before going further it is essential to describe the appearance of the unreduced hernia in the opened sac. The contents of the sac are either cæcum and ascending colon in right hernias, or ileopelvic colon (commonly called sigmoid) in left hernias; very rarely the transverse colon. The sac, well formed and complete on its anterior aspect, is seemingly deficient behind, the bowel being tightly adherent to, and apparently incorporated in, the posterior wall of the sac; hence the designation, hernia with incomplete sac. Fig. 1 shows this condition in sagittal section, Fig. 2 in cross section. If the incision in the sac is carried through the internal ring into the abdominal cavity, it will be seen that the adhesions of the gut to the posterior surface of the sac are continuous with the mesosigmoid, or with the normal reflection of the peritoneum from the bowel to the posterior abdominal wall. An attempt to reduce the bowel will be unsuccessful until it is separated from the posterior wall of the sac by sharp dissection or without reducing sac and gut together. Above all, it is noteworthy that the adhesions between gut and sac wall show no evidence of being inflammatory, but resemble what they really are, the usual adhesions of the large intestine to the posterior peritoneum (Fig. 7).

PATHOGENESIS.

In attempting to elucidate the various theories, I shall speak principally of adherent hernia of the sigmoid, as what pertains to hernias of the sigmoid on the left side may be applied to hernias of the cæcum on the right. I shall first consider the commonly accepted theory, that these hernias are due to the sliding of the posterior peritoneum on the underlying cellular tissue, the peritoneum sliding into the internal ring, carrying with it the attached loop of large bowel. This theory appears untenable, and rightly so,

* From the Annals of Surgery, August, 1913.

Page 496

Figure 1.
Sagittal section of adherent hernia of large intestine, showing adhesions between mesentery, gut and posterior wall of sac.

Figure 2.
Cross section of large intestine, showing adhesions between mesentery, gut and sac wall, with nutrient vessels in the adherent mesentery.

Figure 3.

Cross section through abdomen at third lumbar vertebra, looking toward diaphragm, showing mesentery of ascending and descending colon adherent to posterior abdominal wall.

as it is based upon unsound mechanical principles. The iliopelvic colon or sigmoid is, in part, normally attached to the posterior peritoneum at the level of the left sacro-iliac synchondrosis, by a broad fold of peritoneum, which appears deficient on the posterior aspect of the gut. That is, the posterior surface of the bowel is apparently in direct contact with the retro-peritoneal cellular tissue of the ileopelvic fossa. In a certain number of cases, however, the attachment of the ileopelvic colon lies at a lower level and the anterior leaf of its peritoneal covering is reflected to the anterior abdominal wall, just above Poupart's ligament, the posterior leaf to the posterior abdominal wall just above the internal ring. This brings the posterior uncovered surface of the bowel in direct contact with the internal ring, also uncovered by peritoneum, as its peritoneal covering has been dislocated to the anterior abdominal wall. Any sudden increase in intra-abdominal pressure or prolonged increase, as due to straining at stool, is sufficient to force the knuckle of bowel through the unprotected ring and into the canal. The

Figure 4.   Figure 5.

Figure 4. Alimentary tract of embryo of six weeks, showing rudiments of the two mesenteric systems (after Hertwig).

Figure 5. Embryo of eight weeks, showing large intestine with free mesentery outlining the abdomen.
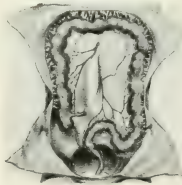
Figure 6.

Drawing from cadaver, showing the adherence of the entire ascending and descending colon, the adhesions beginning at the hepatic and splenic flexures.

continuance of pressure forces the gut, dragging the peritoneum behind it, further along the canal into the scrotum. This low position of the sigmoid is supposedly due to the downward dislocation of the peritoneum lining the lower portion of the abdomen. This dislocation is either congenital or has been caused by increased intra-abdominal pressure. It is presumed that the posterior peritoneum has become loosened from its underlying supporting cellular tissue. This theory, accepted by Ranzi, Scarpa, Wier, Stoney, and many others, is utterly fallacious. Even in the opened abdomen, it is no easy task to strip the peritoneum from the abdominal wall, so close is its adherence; in addition to this, any increase in intra-abdominal pressure only serves to apply the parietal peritoneum more closely to the abdominal wall.

If this form of hernia occurred by sliding of the peritoneum on the posterior abdominal wall, there would be a dislocation of the entire posterior

peritoneum with the attached gut; whereas, the splenic flexure on the one hand, and the hepatic flexure on the other, are invariably found in their normal anatomical positions. It is true, that Tuffier has reported a case of enormous hernia of the descending colon, where the kidney was dislocated. This, however, was probably due to a dragging of the inferior mesenteric artery on the aorta and the dislocation of the aorta and through it a dislocation of the kidney. Again, if this form of hernia occurred by sliding, there would be from the moment of occurrence difficulty in reduction; whereas, in nearly all cases the history points to the hernia having become irreducible only after months or even years.

But most convincing of all are the few cases in which, without visceral transposition, the cæcum has been found adherent in left-sided hernias and

Figure 7.
Drawing from life, showing the sigmoid adherent in the opened sac.

the sigmoid in the right hernias. By the utmost stretch of imagination there can be no discussion on this point; the peritoneum on the left side cannot slide into the right inguinal canal, nor *vice versa.* Furthermore, it is almost axiomatic that the *sine qua non* of the development of a hernia of an intestinal coil is the mobility of that coil. If a loop of intestine is found fixed in a hernial sac, it is conclusive proof that before the formation of the hernia the loop was mobile. The sigmoid does not rest on the cellular tissue of the posterior abdominal wall, but is separated from it by a triplicate layer of fused peritoneum. First the posterior peritoneum itself, second and third the double layer of adherent mesentery through which the nutrient vessels of the gut pass (Fig. 4). This same relationship exists between the sac wall and the adherent intestinal coil (Figs. 1 and 2). This fused peritoneum, called by the French the *fascia d'accolement,* fixes the attached portion of

the sigmoid and cæcum firmly to the posterior abdominal wall, and itself prevents any possibility of sliding or dislocation.

An ingenious, though untenable, theory has been advanced by Lockwood, who claims that before the descent of the testes the right testicle lies in close relationship to the cæcum, the left to the sigmoid flexure. Lockwood supposes that an abnormal adhesion develops between the cæcum or sigmoid on the one hand and the right or left testicle on the other. The testicle in its passage downward through the internal ring pulls on the cæcum or sigmoid, as the case may be, and dislocates it downward to the region of the internal ring, where any slight increase in pressure is sufficient to force the gut into the inguinal canal. The untenability of this theory can be appreciated when it is realized that the extraperitoneal testicle is separated from

Figure 8.

Showing method of operating on adherent hernia of sigmoid: peritoneal flap prepared for closure of ring: purse-string and continuous suture for formation of new mesentery almost completed.

the gut, not only by the parietal peritoneum, but also by the double fused layer of agglutinated mesocolon. In our many cases of retained testes, we have never encountered any such adhesion. It is just as impossible to picture an adhesion occurring between the kidney and intestine as between the testicle and intestine. However, even granting the possibility that this adhesion might occur, the disproportion in size between the testicle and colon would result not in a descent of the colon, but rather in a retained testicle.

Another theory almost too futile to deserve serious consideration has been advanced by Savariaud. He supposes that the bowel slips out from its mesentery as a glove finger is everted, passes behind the peritoneum and so on into the ring. Considering that the true length of the colic mesentery, though adherent, extends from the vertebral column to the gut, this theory becomes immediately disqualified (Fig. 3).

It is evident that none of these hypotheses can adequately or satisfactorily explain the condition under consideration. In order to truly understand the pathogenesis of attached hernias of the large intestine, it is essential to consider the embryology of the intestinal tract, its mesenteries, and particularly the secondary changes in the mesentery of the large intestine.

During the fourth week of embryonic life, the alimentary tract stretches as a straight tube from primitive mouth to anus. All but the upper portion is attached behind to the chorda by a straight double mesentery, the layers of which enclose at the base the primitive aorta. The first differentiation of this tube into its separate parts begins with the development of a small spindle-shaped enlargement, the stomach. The rest of the alimentary tube is still connected with the yolk sac. The further alteration in the shape and position of the alimentary tube and its mesenteries is due to the disproportionate lengthening of the tube, that is, disproportionate to the development of the abdominal cavity. Consequently, to find room, the intestinal canal must take a winding and tortuous course.

The stomach is the first portion of the intestinal tract to begin its axial rotation, turning so that the left side becomes the anterior surface and lesser curvature, the right side the posterior surface and greater curvature. This brings the pylorus slightly to the right of the median line, and begins the twisting of the intestine. The twisting of the small intestine takes place about the origin of the superior mesenteric artery, and both it and the large intestine rotate in the direction opposite to that of the hands of a clock.

In an embryo of six weeks the intestinal tract, greatly increased in length, has already formed two distinct loops both running in an anteroposterior direction. In these loops can be recognized the rudiments of the two mesenteric systems, the great or superior and the lesser or inferior (Fig. 4). From the pylorus the intestinal tube runs directly backward to the vertebral column; from here a sharp bend downward and forward toward the umbilicus; from the umbilicus back to the vertebral column and then straight on to the rectum. The upper loop consists of two nearly parallel arms connected to the vertebral column by a sagittal mesentery, in which runs the first evidence of the superior mesenteric artery. At the apex of the loop is the now occluded viteline duct. A little further toward the caudal end of the embryo is found a slight enlargement, the beginning of the large intestine. At this stage the lesser or inferior mesenteric system can also be distinguished near the caudal end of the embryo. During the third month further changes occur in the size and position of the stomach. As these changes, however, are not germane to the subject under consideration, it suffices to say that the twisting of the stomach and its mesentery results in the formation of the bursa omentalis. The changes in the small and large intestine, particularly the variations in the relation of their mesenteries, are of paramount importance to the comprehensive exposition of hernias of the large intestine. The duodenum is the only portion of the small intestine which

retains its early embryonic position. It is attached to the vertebral column by a short mesentery, which early fuses with the parietal peritoneum, thus permanently fixing the duodenum in place.

The increase in length of small intestine is accommodated by the folding of its mesentery in a frill shape, the base narrow and the outer edge of great length. The most important change, however, takes place in the position of the large intestine and its mesentery. This fact must always be borne in mind; the large intestine at all times possesses a long mesentery and is at no stage or in no part extraperitoneal (Fig. 3). The cæcum is at this stage rotated across the abdomen from below upward and from right to left and again to the right, until it occupies a position under the liver. This ascending loop, which later forms the entire large intestine, thus crosses the loop of small intestine from below upward and from right to left, crossing at the duodenum, carrying its mesentery with it. This explains why the duodenum is buried under the transverse mesocolon (Fig. 5). The cæcum, in the adult sense of the word, is not yet developed, as it is not an integral part of the embryonic large intestine, but a pouching or evagination of its wall. The transverse colon as in adult life crosses the duodenum to the splenic flexure and from there on the descending colon to the rectum. In later embryonic life the cæcum descends toward the right pelvis, forming the ascending colon.

This description has been undertaken to show that the entire large intestine has a distinct mesentery and lies free in the abdominal cavity. The large intestine forms a horseshoe, outlining the confines of the peritoneal cavity. Grouped in the center are the small intestines (Fig. 5). The secondary adhesions, which now form, change the mobile fetal large intestine into the fixed adult type.

Peritoneal surfaces have a tendency to adhere when they are held in contact under pressure. The small intestine, and particularly its mesentery, does not adhere to the parietal peritoneum, for two reasons: (1) From the time of the development of the liver in the fifth week, the small intestines are filled with its secretion, and in a state of active peristalsis; (2) its frilled mesentery presents no broad surface for agglutination.

The conditions in the large intestine and its mesentery are the reverse.

(1) The broad flat mesentery stretching on either side from the vertebral column to the large gut rests directly on the posterior parietal peritoneum (Fig. 4). Moreover as the large bowel is empty and not in active peristalsis, it is immobile.

(2) The mesentery is held in contact to the posterior parietal peritoneum not only by the pressure of the filled moving small intestines, but also by intra-abdominal pressure.

(3) Still another feature is the increase in local pressure at the site of the projecting kidneys and adrenals, which force the parietal peritoneum in direct contact with the ascending and descending colon.

The adhesion of mesentery always precedes the adhesion of the bowel; that is, the adhesions begin at the root of the mesenteries and spread toward bowel. Failure of the adhesions to be continuous results in the ileocæcal fossa on the right side, the parasigmoid on the left (Fig. 3).

The agglutination of the large intestine begins at the transverse mesocolon, which adheres to the great bursa. The transverse colon, however, retains its mobility by the mobility of the bursa itself. According to Browman, the limits of adherence of the ascending and descending colons depend entirely on the retroperitoneal position of the kidney and adrenals. Only those portions of the colon lying directly on the anterior surface of the kidney and adrenals adhere, which accounts for the comparative mobility of the cæcum and ileopelvic colon, both of which lie below the level of the kidney. This explanation of the mobility of the cæcum and pelvic colon, while very plausible, does not explain those cases in which the entire descending and ileopelvic colon is found adherent to the posterior peritoneal wall (Fig. 6). The theory, which seems more plausible, is that advanced by Lardennois, that the secondary adhesions of the large intestine begin at two points: on the right side at the hepatic flexure, at the entrance into the mesentery of the highest branch of the right colic branch of the superior mesenteric artery (Fig. 6); on the left side at the splenic flexure, where the highest branch of the inferior mesenteric artery first enters the descending mesocolon, this adhesion being continuous with the phrenocolic ligament. It is interesting to state here that no matter how great the ptosis or dislocation of the colon, the hepatic and splenic flexures are invariably found in their fixed positions. Beginning at the hepatic flexures on the right side the mesentery of the ascending colon adheres along its entire length, the adhesions increasing in extent as the head of the colon descends. The adhesions begin at the inner border of the mesentery and spread toward the periphery. The cæcum being a pouching of the head of the large bowel has no mesentery and, therefore, does not adhere. The extent of mobility of the cæcum depends entirely on its length; a short cæcum being only slightly mobile will never be found in a hernial sac, while a long, freely movable cæcum has almost the same opportunity of entering the hernial sac as a coil of small intestine. This comparative mobility of the cæcum is often observed during operation in the appendix region. Every operator realizes how simple it is in some cases to deliver the cæcum through a gridiron incision and how difficult in others. The adhesion of the descending colon begins at the splenic flexure and passes progressively downward along the whole course of the posterior abdominal wall to the brim of the pelvis.

It is necessary at this point to consider the measurements of the different parts of the colon. The left colon is arbitrarily divided into the descending and ileopelvic portions. The length of the descending colon is fairly constant, measuring about 14 cm. The ileopelvic portion on the other hand varies within the enormous limits of 14-81 cm. Evidently the longer the

colon the greater will be its mobility, as only that portion will adhere which comes into direct contact with the posterior peritoneum. An extremely long ileopelvic colon partakes of the nature of the small intestine, and for this reason has the same chance of entering the hernial sac. A short colon stretched from the splenic flexure to the rectum would be adherent along its entire length (Fig. 6), and this brings out the crucial point, it could not possibly become engaged in a hernia.

What is the cause of the adherence of the large intestine, when it finally gains access to the hernial sac? Its early reducibility is sufficient proof, that in the beginning it is nonadherent. The reason for its adherence is that under resumed embryonal conditions it follows its embryonal tendencies. In the hernial sac, the broad flat mesentery of the large intestine comes into direct contact with the peritoneal surface of the sac. Moreover, the two peritoneal surfaces are held in contact under considerable pressure, as the large intestine, particularly by pelvic colon, is usually distended with fæces. Beside, the large intestine, unlike the small intestine, is comparatively immobile and seldom in a state of active peristalsis. Thus we have the requisites for peritoneal agglutination present: (1) Broad flat surfaces held in contact under pressure; (2) comparative immobility.

As in embryonic life, the adhesions begin behind, at the attachment of the mesentery, and progress steadily around the sac (Figs. 1, 2, and 7). There are cases reported of so-called hernias without sacs, where the entire sac has been obliterated by these adhesions.

To recapitulate: After studying the embryology of the large intestine and the secondary adhesions of its mesenteries, the following conclusions may safely be drawn:

1. So-called hernias with incomplete sacs do not exist, except as a secondary process.

2. The sac is complete in its incipiency and has been obliterated by secondary adhesions of the embryonal type.

3. A loop of intestine found in a hernial sac is conclusive proof that originally that loop was mobile.

4. In adherent hernias of the large intestine the hernia is primary, the adhesions secondary.

5. The crux of the situation is the redundant colonic loop.

Morphologically, three forms of hernia of the large intestine may be distinguished, the varieties based on the relationship of contents to sac:

1. The sac is complete. That is, there are no adhesions between the sac wall and gut. This form differs in no wise from the ordinary reducible hernias of the small intestine. The loop of the bowel and its mesentery are easily reduced. This form of hernia occurs when from an early stage in its existence the hernia has been kept in place by a truss, and no chance has been given for the formation of adhesions.

2. The most common form of hernia of the large intestine is that with partial obliteration of the sac by secondary adhesions, the so-called hernia

with incomplete sac (Figs. 1, 2, and 7). The posterior portion of the sac has become obliterated by adhesions beginning at the mesentery behind and extending to a variable distance around the sac. The entire loop of bowel is usually found adherent, beginning below at the base of the sac and extending to the neck. When the cæcum and appendix are engaged in a hernia, the adhesion begins at the broad flat mesentery of the head of the colon and the first loop of the ileum.

3. Hernia with complete obliteration of the sac, the so-called sacless hernia, is extremely rare and very few cases have been reported. There is some doubt whether this form of hernia really exists, and whether some portion of the sac, however small, is not always preserved.

These adherent hernias of the large intestine are seldom strangulated, probably due to the large size of the ring, which has been enlarged by the thick-walled large bowel and its semi-solid contents. On the other hand, inflammation and the presence of fibrinous exudates in the sac are not of unusual occurrence, as in Case I. This is perhaps due to an injury of the irreducible gut, and the migration through its wall of bacteria.

On opening the sac by a hernia-laparotomy incision, it is found that the adhesions of the gut to the posterior surface of the sac are continuous with the mesosigmoid, or with the normal reflexion of the peritoneum to the posterior abdominal wall. The gut is continuous with the pelvic colon or with the ascending colon as the case may be. The adhesions are so dense that it seems as though the sac is really deficient behind. What is most important is the fact that the nutrient vessels of the bowel are found in the adhesions. An attempt to separate these adhesions by blunt dissection is unsuccessful. The anterior part of the sac is free, the posterior wall is formed by the loop of gut, which seems to be really incorporated in the wall of the sac, the peritoneum of the sac appearing to be continuous with the covering of the bowel (Fig. 7). There are frequently other contents of these hernial sacs. On the right side the first coil of ileum with its mesentery may be found adherent in the sac, on the right or left side free coils of small intestine. Unless strangulated, the small bowel is easily reduced, leaving the hernial sac with the large bowel attached to its wall. In some instances the adhesions may be so dense as to include the extraperitoneal testicle and cord. Cases have been reported in which the testicle was so adherent that it was necessary to sacrifice it before radically curing the hernia. This, however, seems in the majority of cases unjustifiable.

Symptomatology.—Though the symptoms of these hernias are not in any way distinctive, there are certain suggestive features which point to the possibility of a diagnosis being made. Usually occurring in males, these hernias come on after adult life. At first reducible, they become irreducible after months or sometimes years. If sigmoid hernias, they have a doughy feeling and cause their bearer less discomfort after a thorough evacuation of the bowels. If a hernia of this sort is suspected, the diagnosis could easily be made by the injection of bismuth per rectum, followed by a radiogram. It

is during operation that the diagnosis can and must be made, as only by precisely understanding the condition present can proper treatment be instituted. After exposure and isolation of the sac in a radical herniotomy, it is the practice of many surgeons to attempt to reduce the contents before opening the sac. If this maneuvre is unsuccessful, an immediate suspicion of adherent hernia should be roused, and the greatest precautions taken to obviate injury to the bowel. The sac should be palpated with the gloved finger and a non-adherent portion found, which is invariably in the anterior portion of the sac. Grasping this non-adherent portion of the sac with forceps, it is lifted free from the underlying contents and opened by a small incision. The opening is enlarged upward toward the neck of the sac preceding the incision, with the finger or grooved director. In extending the opening of the sac downward, it is well to exert great care not to injure the cross loop of the bowel. After freely opening the sac, if this form of hernia is borne in mind, the diagnosis can surely be made. If a gentle attempt is made to separate these adhesions, it will be found unsuccessful without using undue force. In fact any attempt to separate these adhesions is unjustifiable and may result in disaster.

Treatment.—According to Weir, Heydenreich attempted this manoeuvre in two cases, both followed by fecal fistula and recurrence of the hernia. Numerous like disasters have been reported. Fearing a similar result, Jaboulay resected the entire adherent loop of bowel.

No matter what method of treatment is followed, it is essential that the neck of the sac should be well exposed. To accomplish this exposure, it is frequently necessary to perform a hernia-laparotomy. This is done by introducing the finger through the internal ring and cutting the internal oblique to a variable extent above the ring. After this is done, one of several methods of treatment may be instituted. Savariaud's method is in fact a reduction of the sac and bowel *en masse*. This method was practiced in Cases I and II. In order to thoroughly complete this operation, the sac and its contents must be well exposed above the internal ring, which must be stretched sufficiently wide to permit the passage of the sac and its contents without using undue force. In his original description of the operation, Savariaud advised the closure of the incision in the sac wall before reduction is attempted. The sac and its contents are then forced through the internal ring as though inverting a gloved finger. The ring is closed by bringing the edges of the inverted sac in apposition by interrupted sutures. The operation is completed as an ordinary herniotomy.

The disadvantages of this operation are the insecurity of the closure of the ring and the danger which always attends the reduction of a hernia *en masse*. That is, there is a possibility of later strangulation within the reduced sac. The operative procedure followed in Case III, which is a slight modification of a method described by Hotchkiss in 1910, seems to offer greater advantages in that it results in a return to fairly normal anatomical relations. After division and thorough exposure of the sac (Fig. 7) it will, as a rule,

be seen that one side of the sac is of greater width than the other. In this event the more ample peritoneal surface is chosen as a flap to cover the ring. In case the peritoneal surfaces are of almost equal extent the mesial portion of the sac should be utilized for this purpose.

The portion of the sac chosen as a covering for the ring is separated by an incision beginning at the bottom of the sac and running parallel to and at least one inch from the gut wall. The flap is completely freed below, left attached above to the peritoneum covering the internal aspect of the ring (Fig. 8). The loop of bowel is now pulled out well through the ring and reflected on the abdomen. The attached flaps of the sac are now united on the posterior surface of the bowel by a fine running catgut suture, thus forming a new mesocolon. The suture is begun above at the cross loop of the bowel by using a wide purse-string suture so as to prevent angulation. After the continuous suture is completed, the loop of bowel is easily reduced. The ring is closed by suturing the prepared flap of peritoneum to the peritoneum covering the internal ring. The margins of the internal oblique, if divided, are exactly approximated, and the operation completed after the Bassini method. Lardonnois and Okinji suggested that as these hernias are due to the mobility of the large intestine, they should be treated by fixing the intestine to the posterior peritoneal wall. After exposing the sac, the neck is well exposed by a hernia-laparotomy and the gut carefully dissected from the sac. The loop of large intestine is then sutured as high as possible to the posterior peritoneal wall as in colopexy. In extreme cases it might be well to combine this procedure with the method of operation described above. In a class of cases presenting so many difficulties, probably no one method of treatment will be applicable to all cases, and a combination of two methods may occasionally be of advantage.

The following cases are from the records of Dr. Joseph Ransohoff and the writer:

Case I. U. L., aged 54. Complained of left inguinal hernia, which had been present for many years, but had only become irreducible during past two years. Examination revealed a left irreducible inguinal hernia, the size of an orange.

Operation (Jewish Hospital, March 7, 1908). Gas-ether anesthesia. After opening the sac the descending colon was found adherent to its posterior wall. The gut and sac were reduced *en masse,* and the ring closed by suture. The operation was completed as a typical Bassini. The recovery was uncomplicated and there has been no recurrence.

Case II. A. L., aged 53. Had had a hernia for two years, which became irreducible during the last two months. During past two days the hernia was swollen, tender and painful. Examination revealed a tense irreducible left inguinal hernia, the size of two fists.

Operation (Jewish Hospital, May 13, 1909). Gas-ether anesthesia. After exposing the sac in the usual way, incision into it revealed the inflamed and thickened sigmoid loop adherent to the posterior wall of the sac.

Gut and sac were reduced *en masse* and the ring closed by the suture of the inverted sac wall. The operation was completed as a typical Bassini. Recovery was uneventful, and there has been no recurrence.

Case III. D. B., aged 59. Had an irreducible inguinal hernia, which had been present for twenty years. During past three years hernia had become irreducible. Examination revealed a very corpulent man with a large, irreducible, left inguinal hernia.

Operation (Jewish Hospital, July 29, 1911). Gas-oxygen-ether anesthesia. After exposing the sac in the usual way, an attempt to reduce its contents before opening was unsuccessful. On opening the anterior part of the sac, a loop of the sigmoid about ten inches long was found adherent to its posterior wall. The neck of the sac was exposed by incising the internal oblique. A peritoneal flap for the closure of the ring was made as described above. The two attached portions of the sac were united over the posterior surface of the gut by a running catgut suture. The gut with its new formed mesentery was easily reduced and the ring closed by suturing the prepared flap to the margins of the ring by interrupted catgut sutures. After carefully approximating the cut margins of the internal oblique, the operation was completed as a typical Bassini. Recovery was uneventful, and there has been no recurrence.

THE DANGERS AND FALLACIES OF INTRASPINOUS INJECTION OF SALVARSAN.*

William Ravine, M. D.

Cincinnati.

In our zeal to combat syphilis of the central nervous system, we are prompted more by enthusiasm and theory than by reason and judgment. Time-honored weapons, which have served us well in our therapeutic armamentarium, are cast aside, to join the ever-growing number of faddists.

The Direct Intradural Injection of Salvarsan.—Wechselman, in 1912, and Marinesco, in 1913, reported unsuccessful attempts at the direct intra-dural injections of salvarsan. Ravaut, however, reports some favorable results from this method. Wile expresses confidence in the method of Ravaut, but points out the dangers of its use; where there are any involvement of bladder and rectum, these constitute for him a decided contra-indication. Gordon reports a most disastrous case following the intradural injection of neosalvarsan, after the method and technique of Ravaut, a synopsis of the case which I will quote: "The patient, a man of thirty-five years of age, presented all the typical symptoms of tabes dorsalis. At the time he came under my observation, pain in the lower extremeties, ataxia, incontinence of urine and constipation were the most conspicuous manifestations. Formerly, I was told, he had the usual course of treatment with iodids and mercury. At this time the Wassermann reaction of serum and spinal fluid was positive. I proposed at once the treatment with auto-salvarsanized serum, which was promptly accepted. The result from one injection was gratifying. The pain had almost disappeared, the ataxia improved, also the incontinence of urine decreased considerably. Constipation remained unaltered.

"For a period of two months the patient felt very comfortable. Soon, however, the bladder disturbance returned. As the Wassermann reaction was at this time positive, the patient finally accepted the offer to have another intraspinal injection, which he had repeatedly refused during the past two months. With the patient's consent, I had recourse this time to the direct intradural injection of neosalvarsan instead of the salvarsanized serum. Accordingly I had the fluid prepared after Ravaut's technique. The solution used was a 6 per cent. neosalvarsan in distilled water. As each drop of the solution contained three mg. of neosalvarsan, only two drops were injected from a specially constructed and very accurately graduated syringe. The lumbar puncture was made with a needle, the end of which fitted the graduated syringe. After a small quantity of spinal fluid had flowed out of the cannula and been collected in a tube for diagnostic purposes, the syringe was attached and the fluid was allowed to run in, in order to mix

with the drug. Then the mixed fluid was pushed gently into the canal. The procedure of mixing was repeated the second time. The patient was then placed in the Trendelenburg position. One half-hour after the injection the patient commenced to complain of severe pains in the lower limbs, which in subsequent days became more and more pronounced. Vomiting appeared on the same day and kept up for six consecutive days. Retention of urine took the place of the former incontinence. Incontinence of feces made its appearance. All these symptoms continued without relief. On the fifth day, small erythematous patches appeared on the glans penis, scrotum and the sacrum. They gradually became larger and finally distinctly gangrenous. Two weeks after the injection the patient presented the following picture: He was unable to stand or walk; he suffered agonizing pains in the lower limbs, so that sleep was impossible; retention of urine and incontinence of feces were exceedingly disturbing; the gangrene of the above-mentioned areas was becoming more and more profound; the temperature reached 102 to 103° F.; he vomited daily, lost his appetite and was losing weight. Gradually the condition grew more and more alarming and finally he expired. This case seems to militate against the direct intradural injection of neosalvarsan, notwithstanding the favorable reports of Ravaut and Wile. Animal experimentation with the direct intradural injection of salvarsan in monkeys had to be abandoned on account of the caustic and destructive action of the drug.

"The direct intradural injection has now been for the greater part supplanted by the ingenious method of the salvarsanized serum injection of Swift-Ellis, for the technique of which the reader is referred to the original article. One thing which all the writers who laud this method over all others forget to mention is this: The main reliance of the Swift-Ellis method lies in the intravenous injection of salvarsan preceding the intraspinous injection, a point which the originators of the method personally mentioned and emphasized to the writer, and quoting verbatim from their original article the following: 'In dealing with syphilis of the central nervous system, we are, however, more fortunate than is the case in purulent meningitis, for here the introduction of our therapeutic agents into the general circulation is of undoubted benefit. With mercury, iodids and with salvarsan intravenously, much can be done, and in many patients all clinical signs and symptoms can be relieved.'"

What is accomplished by the Swift-Ellis method of treatment? Wassermann plus is changed to negative. The number of lymphocytes in the cerebro-spinal fluid is reduced. Globulin reaction becomes negative. In other words, the improvement shown is a biochemical or laboratory improvement. The high cell count and the globulin reactions are the manifestations of an inflammatory process, and it is questionable whether its reduction is going to be a distinct advantage to the patient; we must not lose sight of his general condition. Clinically, no results are reported aside from the

fact that the patients are reported as feeling better. What a variable quantity this is.

This method is not without its dangers, as we are but to refer to the fatalities which occurred at Los Angeles in seven cases after the intraspinous injection of salvarsanized serum. The method is more painful, requiring very often opiates for the relief of pain in the legs. Paralyses of the legs, incontinence of urine and feces persisting for months, and later followed by death.

Sachs reports a case of paresis developing an acute ascending paralysis of Landry after the sixth intraspinous injection, all of the injections having been tolerated with great comfort.

Myerson reports several cases which grew rapidly worse after this method. One case in particular merits its reproduction here.

Case No. 11737.—F. M. L., male, aged thirty-nine years, married; entered May 6, 1913. The occasion of the patient's commitment was the sudden maniacal outbreak in the house of a friend. Family history, negative. Had a high school education. He had been a spendthrift, a heavy drinker, and led a dissolute life. At first he denied syphilis, but later admitted having it years ago. At the time of entrance he was clearly oriented. Memory seemed intact; no hallucinations or delusions were elicited. He was somewhat euphoric. Continually attempted to leave the hospital; rather verbose in answers, otherwise showed no distinct mental symptoms; physical signs were carefully noted at that time. The left pupil was slightly larger than the right; both reacted moderately to light, consensual and distance. Cranial nerves of the face were good. No paralysis anywhere. Slight tremor of the hands; reflexes of the arm were equal and moderate; knee jerks equal and active; ankle jerks equal and active. No Babinski, Gordon or Oppenheim. Adductors moderate; cremasters and abdominals O. K. In other words, physical examination was almost entirely negative. Blood serum positive to the Wassermann reaction to syphilis. Spinal fluid showed moderate pressure, albumin much increased Wassermann negative, globulin by Nonne's method slightly positive, likewise by Noguchi's method; cells mostly red, of which there were perhaps one thousand in the field. No blood had been drawn upon puncture, and these cells, it is evident, had not come from the puncture, since the slightly yellowish tinge of the spinal fluid could not be centrifuged out. This peculiar spinal fluid had its explanation a very short time afterward in the following:

May 11, during the morning, the patient was restless, confused and attempted to get out. At 12:30 he suddenly lost consciousness, became rigid and showed some clonic movements. Recovered in about thirty minutes. During this time there was a double Babinski, more on the right side, rigid pupils, absence of abdominal and cremasteric reflexes. At 6:00 p. m. he was up and around, very euphoric and markedly confabulating. He told how he had been out all day in an automobile, and spoke of the very elabo-

rate meals he had had. Showed marked loss of memory for recent events. Was disoriented for time and place. Gave irrational answers to questions on educational matters. Lumbar puncture done at this time shows that spinal fluid was under high pressure, was yellowish in color, and contained very many red cells, although no blood had been drawn by the puncture, and, as before, the color could not be centrifuged out. The Wassermann reaction in the blood was still positive. At this time there was positive Wassermann reaction of spinal fluid. The globulin was distinctly positive.

From this time, for a period of a month, the patient had marked euphoric delusions. He was to marry a nurse of the ward; he had $50,000, a motor boat, and a Pierce-Arrow automobile was to take him and his bride all over this country and to Europe. He denied that he was married, and said most emphatically that the nurse, who was possessed of all the virtues of her sex, both in character and in person, had promised her hand to him as soon as he could get out. He had schemes for making money. Gradually this euphoric state disappeared.

TREATMENT

May 14, .45 gr. neosalvarsan.

May 21, .45 gr. neosalvarsan.

May 24, 20 c.c. serum intradurally; Wassermann reaction serum positive.

May 28, .9 gr. neosalvarsan; Wassermann reaction serum negative.

May 31, 30 c.c. serum intradurally; Wassermann reaction serum negative.

June 6, .6 gr. neosalvarsan.

June 7, Wassermann reaction, serum slightly positive; 20 c.c. serum injected intradurally. Spinal fluid at this time showed still the slight yellowish tinge, although no red cells were to be seen. This yellowish tinge persisted for some time, and was probably due to hemoglobin and to dissolved coloring matter from the red cells. Finally it disappeared and the fluid became clear.

June 11, .45 gr. neosalvarsan; Wassermann reaction spinal fluid negative.

June 14, Wassermann reaction serum positive.

June 19, .9 gr. neosalvarsan.

June 21, 30 c.c. serum intradurally; Wassermann reaction serum negative; spinal fluid suggestion of positive.

July 2, .9 gr. neosalvarsan.

July 7, 30 c.c. serum intradurally. Spinal fluid at this time, five cells; globulin slightly positive; albumin distinctly increased; suggestive positive Wassermann serum slightly positive.

July 16, .9 gr. neosalvarsan.

July 19, 30 c.c. serum intradurally, ten cells; globulin strongly positive; albumin increased; Wassermann reaction in serum and spinal fluid negative.

July 30, .9 gr. neosalvarsan.

August 2, Wassermann reaction serum positive.

August 9, another physical and mental examination was made. He does not remember the two weeks following the convulsions. Following that, however, his memory is clear. He laughs at his former delusions concerning the nurse, likewise his wealth. He spontaneously states that he has been losing his memory for some time before he came to this hospital, likewise losing his ambition, and that he was cranky at home. No pains; occasional dizzy spells. Physical examination at this time shows very important changes. The right pupil showed almost no reaction to light; the left showed prompt consensual and light reaction. The right arm reflex is lively; greater than the left; knee jerks are equal; right ankle jerk is active; left ankle jerk very slight. No Babinski, Gordon or Oppenheim. Mental examination by the Binet-Simon and Healy tests showed no distinct defects. By careful psychological tests for memory defect, and by the ordinary psychiatric examination, nothing of a pathological nature was found. He took an active part in the social life of the ward, and was one of the leading spirits among the patients.

August 13, .9 gr. neosalvarsan.

August 16, 30 c.c. serum intradurally; Wassermann reaction serum slightly positive; Wassermann reaction spinal fluid negative.

September 13, serum positive; treatment discontinued.

October 29, note was made that his condition was unchanged.

December 24, discharged to the Taunton State Hospital. Diagnosis, general paresis; condition unimproved.

At the time of his discharge from the Psychopathic Hospital, the patient had commenced to become grandiose again. He exhibited eccentricities of conduct, and is said to have had a hysterical outburst. This outburst the patient describes differently. He said he had a numb feeling in his head and in his right hand, that while he knew the words he was to say and use he could not utter them. Neither could he write, although he could read what was brought to him. When he attempted to make himself understood by the physicians he spoke nonsense and realized that it was nonsense. By his description there was a cerebral condition of some kind, transitory in nature, marked by motor aphasia and confusion, with numbness of the right hand.

Physical Examination at Taunton, December 26.—At this time the pupils are Argyll-Robertson on both sides; tremor of tongue; blunting of sensation of right side of face; arm reflexes as before; left Achilles diminished. No Babinski, Gordon or Oppenheim. Cremasterics present. Left upper and lower abdominal absent; ophthalmoscopic negative.

Mental examination at this time shows verbosity, pomposity, euphoria and delusions of grandeur, mostly of a sexual character. He is to marry

a nurse at the Phychopathic Hospital, and they are to go on a long trip together. He is to furnish the home. She is the most beautiful and virtuous of women. Orientation is intact; memory is good; no hallucinations; acts superior to his environment; somewhat irritable and troublesome among the patients; Wassermann reaction in spinal fluid positive; albumin moderately increased; thirty lymphocytes; serum positive.

Summary.—This patient, at first considered a case of cerebral spinal syphilis, is now considered a general paretic. First, the history of cerebral accident; second, the euphoria, grandiose ideas, etc.; third, the gradual development of Argyll-Robertson pupils and the gradual change in reflexes; fourth, the appearance of all the four reactions in blood and spinal fluid plus the albumin increase in the latter. He has shown fluctuations in the Wassermann in blood, and there was present in the spinal fluid evidence of a hemorrhage which has made its way into it. Undoubtedly the first flare up was a hemorrhage into some part of the brain, and it is very probable that the second development of grandiose ideas started with some cerebral attack. It is to be especially noted that the Argyll-Robertson pupils developed in this case despite the use of salvarsan and the use of salvarsanized serum, and for that reason I think this case of crucial importance in determining the value of the Swift-Ellis method.

It is claimed that the value of the Swift-Ellis over any other method lies in the fact of the inaccessibility of the nervous system through the blood stream. The effects of bromide, chloral, opium, alcohol, strychnia, and certain of the toxins of the infectious diseases, seem notably to affect the brain and nervous system through the blood stream.

Professor Benedict, of the Cornell Medical School, made an examination of four specimens of spinal fluid twenty-four hours after intravenous injection of salvarsan (0.4) and found that the spinal fluid contained free arsenic in about one-sixth to one-tenth the concentration in the whole blood. This is a striking fact and is contrary to the usual belief that none of the drug administered intravenously finds its way into the spinal fluid. This same investigator found more free arsenic in the spinal fluid after an intravenous injection of salvarsan than is found in the salvarsanized serum as used for intraspinal injection.

The injection of a serum into the cerebro-spinal space can, and does, affect a condition which is purely meningeal in its involvement. In tabes and paresis, in addition, we have a destructive process present, which condition we should not make worse by the intradural injection; also the general health of the patient must be conserved.

"Forsake not an old friend, for the new is not comparable to him. A new friend is as new wine; when it is old thou shalt drink it with pleasure." Mercury and the iodids have been tried in countless cases and they have not been found wanting. They have in the past, and will in the future, benefit our cases of syphilis.

Pl.   514

The writer has been able to bring about the same cytological and chemical changes that have been accredited to the method of Swift-Ellis, with mercury and the iodids alone, and in some cases combined with salvarsan intravenously.

A case that I treated at the Kraepelin Clinic at Munich will illustrate the changes that can be brought about in the spinal fluid by the use of mercurial rubs, four gm. daily, plus one intravenous injection of .9 neosalvarsan.

Mr. J. W., aged thirty-three, was brought into the clinic by the police, December 11, 1913, who had found him wandering aimlessly about in the outskirts of Munich. Physical and mental examination at the time of entrance revealed the following: He was disoriented as to time and place, there was a marked dysarthria; no delusions of grandeur. Left to himself, he wanders aimlessly about the examining room, bumping into chairs and tables; he understands spoken language, attempts to read, but confabulates; handwriting is unintelligible. Physical examination: Pupils are unequal, react sluggishly to light and accommodation, ophthalmoscopic examination, bilateral choked disc, increased patellar arm and Achilles reflexes; slight Romberg.

Clinical diagnosis, paresis; serological diagnosis was lues cerebri. Wassermann reaction of blood positive; Wassermann reaction in spinal fluid negative, and on larger concentrations positive; globulin reaction was positive. Cells in spinal fluid, 1,042, the largest amount they had ever seen in a case (the serologist who counted the cells with me considered it a typical American finding). He was put to bed and given mercurial rubs, four gm. daily.

December 16, lumbar puncture was done; showed 949 cells; other reactions same.

December 22, lumbar puncture was done; showed 749 cells; other reactions same.

December 25, lumbar puncture was done; showed 367 cells; other reactions same.

December 29, lumbar puncture was done; showed 625 cells; other reactions same.

January 6, lumbar puncture was done; showed 405 cells; other reactions same.

Choked disc at this date is almost entirely disappeared; talks rational and is oriented as to time and place.

January 13, lumbar puncture was done; showed 200 cells; all the other reactions positive.

January 14, he was transferred to the "Quiet Division."

January 20, he was given .9 neosalvarsan intravenously.

January 27, lumbar puncture showed fifty-five cells, with all the other reactions positive.

January 28, his relatives took him out of the hospital against the advice of the hospital staff, but he was entirely clear mentally.

Summary.—(1) Daily rubs of mercury, four gm.; the cell count was reduced from 1,042 to 200, and after one intravenous injection of neosalvarsan it was brought down to fifty-five cells per c.cm. (2) Mentally he had entirely cleared up. (3) Choked disc almost entirely disappeared (4) The Wassermann in blood and spinal fluid remained positive.

Dr. Sachs, of New York, bears out this statement in a series of cases that they have had. It is also interesting to note that in a few cases that were not treated, which showed a decrease in the cell count of the cerebrospinal fluid as well as remissions clinically.

The rationale of treatment in syphilis of the central nervous system is: (1) Conserve the general health of the patient. (2) Increase the leucocytosis of the patient, as we know in this way all infections are combated; this can be done by the injection, subcutaneously, of nuclei acid. Some European investigators believe in placing the patient in an electric light cabinet; in this, produce what they call an artificial fever. (3) K. I. by mouth. (4) Mercury, rubs or deep muscular injections. (5) Salvarsan or neosalvarsan intravenously or over the fascia lata. (6) Periods of intermission of the anti-specific treatment for one of tonics.

Summary.—(1) The direct introduction of salvarsan and neosalvarsan into the spinal canal has been almost entirely abandoned, as it is fraught with the greatest amount of danger. (2) The chief reliance in the Swift-Ellis method is in the initial intravenous injection. (3) The nervous system is accessible through the blood stream as arsenic is recovered from the spinal fluid after intravenous injection of salvarsan. (4) The amount of arsenic injected by the Swift-Ellis method is only infinitesimal, and the changes brought about are no doubt due to the initial intravenous injection, or to the repeated lumbar punctures, or to the dilution of the cerebro-spinal fluid. (5) The changes brought about by this method are only those of the laboratory; clinical recoveries are not reported; fatalities have resulted and cases have been decidedly made worse. (6) This method has not supplanted the time-honored use of mercury and K. I., plus our new addition, salvarsan. (7) The method is one that requires the greatest care as to asepsis, requires a full laboratory equipment, and can only be used in a well-organized hospital, and is not applicable for the general practitioner. It is very painful, opiates having to be given to relieve severe pains in the extremities.

BIBLIOGRAPHY

The Treatment of Syphilitic Affections of the Central Nervous System with Especial Reference to the Use of Intraspinous Injection. Swift-Ellis, Archives of Internal Medicine, Vol. 12, No. 3, page 331.

Results of the Swift-Ellis Intradural Method of Treatment in General Paresis. A. Meyerson, Boston Med. and Surg. Jour., May 7, 1914, page 769.

Unfavorable Complications Following an Intradural Injection of Neosalvarsan. Alfred Gordon, Jour. A. M. A., November 21, 1914, page 1881.

The Intraspinal Treatment of Syphilis of the Central Nervous System with Salvarsanized Serum of Standard Strength. Hanson & Gechie, Jour. A. M. A., November 28, 1914, page 1930.

Modern Method of Treatment of Syphilis of the Nervous System: Sachs-Straus-Kaliski, Am. Jonr. Med. Scs., November, 1914, No. 512, page 693.

ON THE STRICTURES OF THE MALE URETHRA.*

A. RAVOGLI, M.D., F.A.C.S.,

Cincinnati.

Anatomy.—The male urethra consists embryologically of two parts, a posterior segment beginning at the bladder and ending at the ejaculatory ducts, and an anterior segment which comprehends the remainder of the canal. Considering the regions of the body in which it lies the urethra can be divided into pelvic, perineal and penile portions. In relation to strictures it is beter to consider the urethra as of prostatic, membranous and spongy portions. An abnormal narrowness of any portion of the canal of the urethra constitutes a stricture. Indeed, a simple hardening of the mucosa of the urethra is capable of forming a stricture. The urethra is not a simple canal to let the urine pass, but it acts like a valve, which with its muscular layers squeezes out the urine to the last drop. When the mucous membrane has been hardened and changed in its delicate structure, if yet there is no organic narrowing of the organ, yet the hardened mucosa prevents the last drop of urine from coming out, one or two drops of urine remain beyond the hardened mucosa and maintain a constant irritation which constitutes the so-called gleet.

The urethra has not the same calibre all the way through. The meatus, the middle of the pars pendula and the beginning of the pars membranosa are naturally somewhat narrower. Other parts of the urethra are enlarged, so after the meatus the fossa navicularis is much larger, before the pars membranosa is another enlargement forming the bulbar urethra, while the prostatic portion is an enlargement in the shape of a triangle. At this point the ejaculatory ducts and the prostatic ducts open, and from this point infectious materials reach those organs. The pars membranacea runs from the prostatic portion to the bulb going through both layers of the triangular ligament, surrounded by the fibers of the compressor urethræ muscle. Behind it the glands of Cowper lie, the excretory ducts of which open at this point in a narrow space the least distensible of all parts of the urethra. This is just in the curve, less movable because it is firmly fixed to the symphysis. On account of its curve the anterior wall of the mucosa is shorter than the posterior.

The wall of the urethra is formed by a mucous membrane containing a rich venous plexus, and in the prostatic and membranous tract it is well clothed with muscular tissue. The mucous membrane has an epithelium which varies in the different parts of the urethra. The proximal two-thirds of the prostatic portion resembles the epithelium of the bladder. At the pars membranacea the epithelium takes the aspect of the columnar type. This epithelium covers the rest of the urethra to the fossa navicularis,

where it is changed into stratified epithelium. The meatus is the continuation of the epidermis covering the glans.

The muscular fibers are some striated and some non-striated. The non-striated, involuntary, are incorporated in the wall of the urethra, while the others are in the form of accessory bundles derived from structures surrounding the urethra. Some of the intrinsic muscles are longitudinal, forming the first coat, and some are transverse or circular. The circular fibers, well developed, form a thick layer especially towards the internal orifice. The removal of all urine at the end of micturition is due to the action of the muscular tunic.

Varieties.—Stricture may be spasmodic the result of the contraction of the compressor urethræ, which may impede temporarily the passage of the urine from the bladder. Keyes[1] refers to this condition—the abnormal urination in nervous individuals, who can not urinate in the presence of others. After an operation for hemorrhoids in some individuals the urination becomes difficult and spasmodic. This kind of stricture is not permanent, being only of spasmodic nature, yet it must be relieved to avoid disastrous consequences in the urinary organs. In these strictures the use of the filiform bougies will increase the irritation while a good size catheter will be easily passed and will tire the spasms of the muscle. In withdrawing the instrument no grasping is found. Sometimes, however, a spasmodic stricture co-exists with an organic one and the spasmodic stricture may be the result of the other.

The spasm is easily overcome by the use of hot sitz bath, by the administration of opiates, and later by the insertion of a metallic sound. To prevent recurrence the passage has to be dilated, the muscle stretched, and in order to diminish the sensitiveness, the instillation of a few drops of a solution of silver nitrate 1 to 1,000 will be of a great value.

The strictures which we shall consider here are the sequel of urethritis. They consist in a contracting periurethral formation of fibrous tissue, after the reabsorption of the infiltrating elements deposited in the submucous layer during the inflammatory process. The mucous membrane becomes hard, thickened in some places; the lumen of the urethra is not narrowed, but yet the function of urination is impaired. This can be considered the first stage of the stricture. When, however, the process of infiltration in the submucous tissues heals, on account of the sclerotic changes in the connective tissues, it forms a scar, which retracting the tissues causes the narrowing of the lumen of the urethra. Consequently there are two kinds of strictures: the first soft, easily yielding, which rarely affects the dimension of the urethra, have been called after Otis *wide caliber strictures;* the second kind, formed by hard retracting tissue, have a tendency to narrow the caliber and are known as organic strictures.

It is a difficult task to state when the large caliber stricture begins and when it ends, but it is true that the large caliber stricture is the beginning and the callous stricture the end. A stricture can be formed in any part

of the urethra, but some parts are more subject to the strictures than others. Thompson reported 320 cases of strictures of the urethra of which 54 were seated in the beginning of the urethra from the orifice to two and one-half inches of the pars pendula; 51 were in the middle of the pars pendula; 216 were found in the subpubic curvature in the bulb and in the membranous urethra. The frequency of strictures in these regions is due to the fact that they are exceptionally vascular, and on account of the curve the chronic urethritis is apt to localize at those points. The abundance of follicles in the bulbar region favors submucous exudation. Traumatic stricture is found more often in the membranous urethra.

A stricture may be formed in ten or twelve months after the apparent cure of urethritis, while others are noticed a period of years afterwards.

Etiology.—Strictures may be produced by trauma or by gonorrhea. According to Thompson and Martin those from gonorrhea are much more frequent than the others. As a result of urethral chancre and from ulcerated gummata we have seen deformities of the meatus and cicatricial formations of the fossa navicularis, but it seems that stricture of the urethra proper is chiefly the consequence of a gonorrheal process.

A stricture may be alone, but not rarely do we find more than one stricture in the same urethra. Although Thompson in his statistics amongst 270 cases of strictures has found only 44 cases of multiple stricture, yet Guyon has established as a rule, that strictures of gonorrheal origin are multiple, while those of traumatic origin are single. In our experience with strictures of gonorrheal origin we have found only rarely two at a distance from each other in different portions of the urethra. In some cases a gonorrheal stricture may present a number of ridges to the exploring bougie and so give the sensation of multiple strictures while pathologically it is one.

Gonorrheal strictures are much more frequent than traumatic. Thompson placed them at 75 per cent., Martin at 85 per cent. Gonorrhea itself is sufficient to produce stricture and this is the cause in most of the cases. In some cases, however, the stricture may have been caused by gonorrhea and trauma together as in the injuries of the urethra resulting from the superstitious suggestions of breaking the chordee, or from caustic injections, or from the injudicious use of instruments.

Traumatic strictures have been found to be the result of a fall on the perineum. Prezzer[2] referred to the observations of Millee of seven cases of urethritis caused by riding on the bicycle, and two cases of ruptures of the urethra followed by stricture. In individuals who have practiced masturbation stricture has been found, being the result of tearing of the mucous membrane in the spasm of the pernicious act.

Pathogenesis. It is easy to understand how a stricture is formed in a portion of the urethra, by remembering the changes, which the conjunctiva undergoes in a case of gonorrheal opthalmia. The gonococci after producing acute urethritis, have an inclination to enter the epithelial cells, and, going

through them, find shelter in the deep epithelial layer towards the connective tissues. Usually they limit their action in limited portions of the urethra, where they are less disturbed, as in the glands lacunae Morgagni, in the places where the walls of the urethra are closer together as at the beginning of the bulbar region. A chronic inflammatory process results with an infiltration, which, together with the irritation of the connective tissues of the subepithelial layer, starts the papillary proliferation. At this point by means of the urethroscope the mucous membrane appears dark red, granulated, it is somewhat thicker, hard and inelastic. This is the beginning of a wide-caliber stricture. In some cases in the spongious tissues a kind of inflammatory knot is formed, very painful, hard to the touch. This usually does not form an abscess, but is reabsorbed. When the infiltration disappears the affected trabeculae of the spongious tissue shrink. Their connective tissues, hardened, undergo a sclerotic process. This causes atrophy of the spongious body with narrowing of the lumen of the urethra, and formation of the stricture.

It is not always an acute process which causes infiltration of the trabeculae of the spongious tissue, but more often a chronic inflammatory process is equally responsible for the induration and the infiltration of the spongious tissue of the urethra. This process which can be diffused through a great tract of the urethra is usually limited to a small portion. (See illustration.) The process consists in the increase of the connective tissues of the trabeculae, which makes the alveoli much smaller, and the delicate spongious tissue is converted into a hard and thick degenerated sclerotic tissues.

The work of Vajda, Neilsen, Baraban, Finger, Wassermann, Nadli and Guyon have contributed a great deal to clearing up the pathology of strictures. It seems that the anatomico-pathological process is the same throughout, which from the chronic urethritis gradually brings about the stricture. In the urethritis we find an inflammatory process, which is localized in spots, affecting the epithelial and the subepithelial tissues. In the beginning the acute stage produces infiltration of serum and of small white cells, which infiltrating the connective tissues causes their proliferation and so their thickening and swelling. Gradually the infiltrating cells are reabsorbed, spindle cells go on forming connective tissue bundles, which are changed into a thick succulent superficial cicatrix covered with an abnormal epithelium. When these alterations have diminished the elasticity of the urethra in its deeper layer, and when the cicatricial formation has extended to the corpus spongiosum, then the portion of the urethra loses its elasticity, its normal caliber is narrowed and the organic stricture has formed.

Of course that portion of hardened mucosa retains a few drops of urine which remaining behind the impediment irritate the mucosa and maintain a certain degree of irritation. Guiard[3] thought that the virulence of the urethritis was the cause of the production of the stricture. We have often found strictures following cases of urethritis, which on account of their mildness had been neglected.

The strictures have been described as linear, annular, irregular, tortuous, etc., which are only clinical distinctions to indicate the quantity, the shape, the disposition of the scar tissue, which at times forms a thin band and at other times an irregular mass.

A stricture, post-mortem, appears yellowish-white in color, hard and fibrous in consistency, of different sizes and shapes. It has no hyperemia, swelling or infiltration when seen through the urethroscope during life. The epithelium is thickened, whitish and resembles a superficial cicatrix. The sub-epithelial tissue when the swelling is gone does not show much change, microscopically, but in some cases its surface is ridged, uneven and even nodular. When the stricture has been much advanced a band of cicatrix replaces the mucous membrane, penetrating into the corpus spongiosum. Behind the stricture the canal of the urethra is distended, abraded and superficially eroded.

Microscopic examination shows the epithelium thickened, its cylindrical cells in condition of mucoid degeneration. Pus cells are found imbedded between the layers of the epithelium (Finger[4]). The thin cylindrical epithelial cells are converted into a hard thick pavement-like epithelium. The change of the cylindrical into plaster epithelium is of itself a cause of necrosis of the mucuos membrane, which is connected with the alteration of the subepithelial connective tissues.

In recent cases the infiltration surrounds the lucunae and the glands, which imbedded in the sub-epithelial tissue, after a while become atrophic and disappear. In many cases the inflammatory process remains superficial and produces only a superficial non-constricting cicatrix. In other cases the process is deep, affects the periurethral tissues as far as the corpus cavernosum and forms a thick retracting stricture, as a result of cavernitis complicating the chronic urethritis.

There is a great difference in the amount of retraction between strictures of large caliber and those narrowing the canal. In the first a superficial thickening of the mucosa and the superficial layer is formed, which deprives the portion of the organ of its elasticity and retains a few drops of urine, maintaining a constant irritation. The others, thick, hard, deeply contracted, will scarcely admit a slender sound.

Symptomatology. The symptoms from which we ascertain the presence of the stricture in the urethra are some suggestive, some subjective and some objective or physical.

A long-standing gleet will suggest the presence of a stricture. The patient in the morning squeezes out of the meatus a little drop of clear or milky or even creamy fluid. In some cases the fluid is scarcely perceptible, becomes dry and sticks the lips of the meatus together. In many cases of stricture the gleety discharge is missing.

Whether a gleety discharge accompanies the stricture or not, the urine shows the presence of shreds. These are small, short, or like a light cloudi-

ness, while at other times they are heavy, thick, twisted and soon sink to the bottom. On account of the increased acidity of the urine, the stricture is irritated and contracts, then the symptoms of posterior urethritis grows worse, and the urine becomes cloudy. These exacerbations are considered by the patients as new attacks of gonorrhea.

At this point the patients suffer from what is called irritable bladder, with the necessity of urinating frequently (Hirsch[5]). It is not the nervous bladder but a catarrhal inflammation extending from the posterior urethra to the neck of the bladder, which causes the necessity to urinate, when it is touched or slightly distended by the urine. The frequency or urination varies, and it is felt especially at night, compelling the patient to get up several times to empty the bladder.

The presence of urine in the bladder, on account of the irritability of the genital organs, causes frequent erections at night, which, although not accompanied with loss of semen are troublesome to the patient. In some cases the patients have frequent loss of semen. At times the erections are painful, the stricture prevents the discharge of semen in the sexual act, which either dribbles out of the urethra or runs back into the bladder and is discharged with the flow of urine. In many cases of stricture the patients complain of diminution of the sexual appetite and some of impotence.

Subjective Symptoms—A stricture in the urethra impeding micturition causes change in the stream either during the whole urination, or at the beginning or at the end. The size of the stream may be reduced sometimes to a mere thread. Often the stream is divided into two, spurting in different directions, at times it is tortuous or twisted. The projection of the stream, which is the result of the intensity of the contraction of the detrusor vesicae is greatly impaired, and the last drops which remain behind the stricture dribble out without any force of expulsion. In some cases the urine begins to flow, then stops and the urination is finished at intervals. Painful micturition as a consequence of stricture is rare, and exists only when cystitis or prostatitis has developed, or when the urethra on account of inflammation is sensitive to distension. When the posterior urethra is inflamed pain is felt in the beginning of the urination and at the end, when the last drops are expelled.

When the bladder, still normal, cannot empty on account of the strictured urethra, this may cause spasmodic pains. The pain from the bladder radiates towards the rectum and the urethra. Only in rare cases the stricture may lead to retention of urine. It is the result of an engorgement of the peristrictural tissues, which arrest the normal emission of the urine. According to Valentine[6] this condition is precipitated by alcoholic or by sexual debauch.

It has to be remembered that on account of the continuous straining to urinate, the patients are subject to hemorrhoids and also to rectal prolapse.

In severe cases of stricture the bladder undergoes a process of inflammation not only catarrhal, but parenchymatous in character. The ureters and kidneys are also badly affected by the continuous pressure, and may be involved in a form of pyelonephritis. The presence of the urine back of the stricture forms a dilatation, which may let the urine infiltrate causing extravasation, perineal abscesses, and urinary fistula.

In many cases the stricture of the urethra is responsible for sexual neurasthenia, pruritis of the perineum and rectum, persistent and recurrent herpes progentalis, and even dyspepsia and pains in the stomach.

Objective symptoms are all positive signs which we obtain by means of instruments. It has to be remembered that when discharge is present, it has to be examined microscopically. If there are gonococci in the secretion it is dangerous to introduce instruments. In this case it is better to have the patient treated by the irrigation method.

When no more gonococci are present or no more secretion and the patient shows irregularity in urination, in order to ascertain the presence of the stricture and its location, we introduce a blunt steel sound. The first time we use a sound which easily enters the meatus (10 or 12 American) which, after having been sterilized and well lubricated is introduced with great gentleness.

In some cases the sound is introduced without encountering any obstruction until the bladder is reached, but when the instrument is withdrawn it is grasped so that it can only with difficulty be taken out. This symptom shows the presence of a wide caliber stricture. Before concluding that there is a stricture, the possibility of urethral spasm has to be eliminated. In some cases the irritation from the presence of the sound provokes a reflex action of the muscles of the urethra which, contracting, grasp the instrument. This constriction, however, is never so firm and permanent as an organic stricture. Furthermore, when the constriction is the result of the stricture a discharge of one drop of mucous milky secretion follows the withdrawal of the sound. This drop of secretion is of urine, mucous, saline particles of the urine, which had remained behind the strictured point, and when the sound has distended the stricture it finds its way out of the canal.

In some cases, in order to ascertain the presence of a wide-caliber stricture, it is better to use an olive-shaped bougie, as recommended by Pousson[7], Jurquet[8], and Valentine[9]. The olive-shaped bougie is easily introduced, but when withdrawn it is grasped firmly by the strictured portion of the urethra. In other cases, when the stricture has already impaired the lumen of the canal an obstruction is encountered which prevents the introduction of the sound. Then it is necessary to try smaller blunt sounds until it is found possible to pass the stricture.

When the presence of a stricture has been ascertained it can be easily located in the different portions of the urethra, and can also be measured by means of olivary bougies, or by the urethrometer of Otis. In reference to

this instrument Lovenhardt[10] and Stewart[11] caution the surgeon that it is dangerous and questionable practical utility.

Prognosis.—In a general way we may state that strictures of the urethra do not occur as after as is commonly believed. Jurquet in 1,420 patients with diseases of the genito-urinary tract found 133 cases of strictures of the urethra of which 25 were of large caliber. From our own experience we can assert that the incidence of strictures has greatly diminished. The active propaganda on social hygiene, the exact knowledge of the cause of gonorrhea, and the judicious and rational treatment at the reach of every practitioner have had a great influence in this diminution. Von Sehlen[12] wrote that the formation of a stricture is scarcely possible when a well-directed treatment for gonorrhea is applied. To this has to be added, when the patient applies early to the physician, and when the physician has thorough knowledge of the treatment.

In reference to the stricture itself we can say that the prognosis depends upon the nature and the location. Traumatic strictures have a tendency to contract rapidly, while gonorrheal strictures have slow course. Strictures of the perineal urethra are more difficult to treat than those of the pars pendula. When a stricture is extensive and deep, having its base in the cavernous tisues, it will never be completely cured. It will be relieved by the use of sounds or by operation, but it will gradually relapse.

As to danger to life, it has only rarely occurred that a stricture has caused death. In rare cases death has been the result of extravasation of urine, followed by abscess and gangrene. In other cases death has been produced by chronic uremia, when the kidneys have been involved in an inflammatory process. In other cases death may be the result of cachexia and exhaustion from pain and from the torments caused by an old impassable stricture. The patients lose sleep, fail to eat from the unrelieved desire to urinate, and from the fatigue and the labor of difficult urination.

Treatment.—The treatment of urethral strictures has for its aim to enlarge the lumen of the urethra and maintain its enlarged caliber by dilatation.

Dilatation is effected gradually and gently by the use of sounds, which massaging the scar tissue of the stricture provoke its absorption. Keyes stated that the maximum of effect is produced by the minimum of effort, which coincides with the opinion of Guyon, that the effect is due not to the pressure of the sound, but to its mere contact. Passing a sound by force, will tear and bruise the mucous membrane and consequently increase the inflammatory reaction. A steel sound must go in without effort. In this way the presence of the sound will be able to lessen the congestion at the point of contact, correct the irregularities in the canal and stimulate the deeper tissues to a reaction so as to soften the cicatrix. In our practice we have entirely abandoned the method of forced dilatation and of divulsion, which some years ago were largely applied with serious consequences.

When the stricture is yet soft or in a semifibrous stage, it can be easily removed by prompting the reabsorption of the infilerated elements by means of gradual dilatation.

The dilator of Oberlander marked a great progress in the therapeutics of strictures. It was found, however, that the two blade dilator was not sufficient. Kollman has given us his admirable dilator, which consists of four blades which open in opposite directions. The instrument when closed is not larger than an ordinary sound 22 Charrière. It is introduced in almost any urethra without the necessity of meatotomy. We have used the dilator quite often for many years, but gradually we are using it less frequently, relying mostly on the use of steel sounds.

In cases of hard, cicatricial strictures it is not easy to enter with dilators. Some of these small caliber strictures scarcely admit a sound less than 15 French, others admit only a filiform bougie. The treatment begins with small soft rubber bougies; steel sounds have to be avoided because of the danger of producing false passages. In the treatment of these strictures we have found beneficial the application of electrolysis, for with it we have accomplished in one siting that which we could have obtained only in weeks' treatment. Mansell Moullin[13] claims that in a narrow cicatricial stricture a current of 10 to 15 milliampères has made the scar soft, and the tissues capable of distension. The action of the weak currents produces a serous exudation, and a real decomposition of the fibrous tissues removing the hydrogen with the kathode. Strong currents have to be avoided as they cause cauterization of the tissues. For ordinary work a current of from 10 to 20 M. A. is sufficient. The electrolytic sound is kept at the place of stricture, pushing it gradually and gently forwards. After a short time it is noticed that it advances and the stricture is passed. When the sound has passed the stricture, it is left from three to five minutes, then is withdrawn. The pain accompanying this operation is so insignificant that there is no necessity of local anesthesia. The reaction is somewhat more than that which follows the introduction of an ordinary sound. The softening of the stricture is only temporary, and the use of steel sounds has to be continued to insure a permanent cure.

Levin[14] proposes short radium applications through the urethra as an adjuvant to instrumental dilatation. But a beneficial effect is denied by Ayres,[15] who in two hard strictures used a capsule of 40 mm. left in situ for thirty minutes. In one case retention developed and in the other acute urethritis. In both cases the strictures were harder than before. In obstinate and recurring strictures it is necessary to resort to urethrotomy. Internal urethrotomy in the perineal portion of the urethra is done with the dilatation urethrotome of Otis or of Maisonneuve. The cutting of the stricture is not free of any danger, as sometimes there may be hemorrhage. The benefit is temporary; after a while the tissues shrink again and the stricture needs to be dilated.

In some cases of impassable stricture external urethrotomy by perineal section is the only means to relieve the patient. We have had occasion to perform this operation, many times, with beneficial results.

When by any method the dilatation of the stricture has been obtained the second interesting part of the treatment is to keep the stricture dilated and finish the treatment. For this purpose the passing of sounds with Benequé-Guyon curve, leaving each in for three to five minutes answers the purpose. In a general way we can state that when a stricture of the urethra has been dilated to a caliber of 25 to 30 French it can be considered a good result.

During the treatment of a stricture complications may arise which we shall only mention—epididymitis, inflammation of the stricture, and the so-called urethral fever. The use of internal urinary antiseptics such as salol, formaldehyde ammoniate, known as cystogen, antiseptin or uretropin, will clear the urine and will prevent septic fever. Before and after the dilatation an irrigation with a mild solution of biborate of sodium or of permanganate of potassium will diminish the danger of epididymitis.

The last remedy to save trouble is the hands of the surgeon, thorough sterilization, and from beginning to end, gentleness.

REFERENCES

1. Keyes, E. L. The Surgical Diseases of the Genito-Urinary Organs. New York, 1903, p. 167.

2. Pezze: Ann. des Maladies der Organes Genito-urinaires. 1891. Ref. Monats. f. Pract. Dem., Bd. xviii, p. 58.

3. Guiard: Les Urethrites Chroniques chez l'homme. Paris, 1898.

4. Finger, E.: Blenorrhea of the Sexual Organs. 1894.

5. Hirsch, M.: Die Reizbare Blase. Centralbl. Grenzgebiete der Med. und Chir., 13, 14, 15, 1904.

6. Valentine, F. C.: Vesical Retention of Urine. Medical News, June 18, 1904.

7. Pousson: Large Retrecissements de l'urèthre.

8. Jacquet: Retrecissements urethraux de large Calibre. Ann. des Mal. des Organes genito-urinaires, 1894, No. 4.

9. Valentine: l. c.

10. Lövenhardt: Kongress der Deutschen Dermat. Gesellschaft. May, 1894; ref. Monatsheft. f. Pract. Dermat., Bd. 18, p. 615.

11. Quoted by R. W. Taylor: The Pathology and Treatment of Venereal Diseases, 1895.

12. Von Sehlen: Zur Frühbehandlung der Gonorrhea. Monatscheft f. Pract. Dermat., Bd. xviii, June 15, 1894.

13. Mansell Moullin: Treatment of the Strictures of the Urethra by Electricity. The Lancet, 1893. No. 36, ref. Monat-cheft f. Pract. Derm., Bd. xviii.

14. Levin, Isaac: The Scope of Radium Therapy in Diseases of the Genito-Urinary Organs. The Urologic and Cutaneous Review, Vol. 22, No. 1, Jan. 1918, p. 7.

15. Ayres, Winfield: l. c. p. 1.

A CASE OF TIN POISONING.*

Moses Salzer, M.D.,

Cincinnati.

January 29, 1917, H. M., a traveling salesman, aged 50, consulted me on account of a feeling of coldness or chilliness and sore throat. He said that he had felt chilly for a week or more. His temperature was 102.5 and his throat was red. His tongue was very much coated. He had a full upper and lower set of false teeth. The physical examination was otherwise negative. I sent him home and told him to go to bed. The following day I called on him. His temperature was still over 102, and both tonsils were covered with white spots. A diagnosis of acute tonsillitis was made at this time. In four days his temperature was normal, his throat had cleared up, and I discharged him as cured.

February 21, or three weeks later, he again consulted me, saying that he was not a bit better and that he had had to discontinue his business trip because he felt bad. He still felt chilly. This chilly feeling would be relieved occasionally by hot flashes. On arising in the morning, he said that he felt as if he were stepping into a tub of ice-water. His throat also continued to annoy him. He had indefinite, vague pains in his extremities and the back of his head. The examination of his throat was negative. He said that this feeling of coldness was so persistent and annoying that he was unable to eat, sleep or attend to his business. His tongue was still heavily coated. His blood showed 3,500,000 red, 6,200 whites, and 70 per cent. hemoglobin, but there were no morphologic changes. Repeated examination failed to reveal anything outside of this slight anemia. The Wassermann and Hecht-Weinberg tests were negative.

March 3, Dr. Roger S. Morris saw him in consultation, and was unable to throw any further light on the case. We both agreed that the condition was one of simple anemia following the attack of fever and sore throat in January, and advised that he go to Old Point Comfort for a rest. He did not go, but continued to consult me daily or oftener. His chief complaints were the feeling of coldness and the soreness in his throat. Drs. Iglauer and Allen both examined his throat, and their findings were negative. His temperature was always normal.

March 22, he returned with the same complaints, coldness, irritation or pain in his throat, and indefinite pains in his legs, arms and head. I examined his throat again but found nothing. I told him, however, that I would touch his throat up with some silver nitrate. He then took out his lower set of teeth, and, seeing that they attracted my attention, he said that the teeth were set in tin. This statement was confirmed by his dentist, who stated that the plate was made of Watt's metal, which is two-thirds tin and one-third bismuth. Immediately the possibility that the case was

one of tin poisoning flashed through my mind, although I had never heard of such a case. I reasoned, however, that if other heavy metals could produce poisoning, possibly tin also could do so. The patient had been wearing this lower set since December 11, 1916, or about one month before the symptoms began. I told him not to wear the lower set of teeth, which showed evidence of corrosion in spots, until I had an opportunity of looking up the literature on the subject.

The literature abounds in references to so-called tin poisoning in which tinned foods were partaken of. The symptoms in these cases were confined to the gastro-intestinal tract and were those of an acute poisoning. I was able to find references to only two cases in which tin had been absorbed and had given rise to constitutional disturbances, and one of these was reported by Jolles[1] in 1901. His patient showed constitutional disturbances due to wearing silk stockings impregnated with tin salts. In this case the predominating, outstanding symptom was this feeling of coldness which my patient complained of. Jolles proved that his was a true case of tin poisoning by finding tin in the urine of his patient.

In my own patient the urine passed on the day following the discontinuance of the wearing of the plate contained traces of tin. No other specimens of the urine showed any traces. The patient was placed on a diet free from canned foods, and a few days later the stool was examined. Approximately 5 gm. of dried stool contained 0.0021 gm. of metallic tin. Several subsequent examinations of the stool showed the presence of tin.

April 6, 1917, or fifteen days after the patient had discontinued wearing the plate, 13 c.c. of the blood contained 0.0015 gm. of tin. No other foreign metals were found in the blood. The patient still complained of the same symptoms, although they had ameliorated somewhat. The coating from his tongue had almost disappeared. Considering the marked affinity of tin for proteins, it is not remarkable that the symptoms continued. I prescribed potasisum iodid then, and on the 13th of April, or one week later, 20 c.c. of his blood contained only 0.0005 gm. of tin, showing that more than two-thirds of the tin had been eliminated during the week. No subsequent examination of the blood, urine or feces showed any traces of tin. The anemia gradually cleared up.

The chemical analyses in this case were made by Mr. F. C. Broeman, consulting chemist, and also by Mr. Clarence Bahlman, of the Cincinnati Department of Health. They made their tests independently, using parts of the same specimens, with identical results.

Considerable experimental work has been done with regard to the effects of tin salts when administered to animals. Salant, Rieger and Trenthardt[2] showed that after subcutaneous injections of soluble tin salts, tin was found in the urine, feces, skin and liver. The gastro-intestinal tract was shown to be the chief organ for the elimination of tin.

[1] Jolles: Wien. med. Presse, 1901, 42, 490-509.
[2] Salant, W., Rieger, J. B., and Trenthardt, J. L. P.: Jour. Biol. Chem., 1913-1914, 17, 265.

Ungar and Bodlander[3] and Lehman[4] showed that repeated injections of small quantities of tin into animals, over prolonged periods, resulted in the death of the animals. The effects were manifested in the alimentary tract, the general nutrition, and, above all, in the central nervous system. Paralyses of the extremities were frequently observed.

In an experiment conducted by Schryver,[5] a dog, weighing 8.5 kg., was given 20 mg. of tin subcutaneously in the course of several days, and the animal was then killed. The brain and cord of this animal weighed 65 gm. Twenty gm. were submitted to examination and contained 1.5 mg. of tin.

It is apparent from the foregoing that tin must have a rather strong affinity for nervous tissue.

I lost sight of the patient, and did not see him again until September 14, 1917. He came to me complaining of the same symptoms, but in a milder form. He said that he had been under the care of Dr. Marion Whitacre, by whom he had been sent to Dr. Mithoefer, who, July 12, 1917, removed his tonsils and reported both badly diseased. I saw the patient again, October 17 and November 1, and he was still complaining of the same symptoms. He was, however, attending to his business and his appetite was normal.

This patient has since passed from under my care, and the last I heard of him he was making the "rounds" from one physician to the other still complaining of his "hots and colds," although he is now able to attend to business.

The onset of the symptoms within a few weeks of the patient's starting to wear the Watt's metal plate, and the finding of the tin repeatedly in the blood, stool and urine by two chemists working independently of each other, and then the disappearance of tin from the blood after the patient discontinued the wearing of the plate are to my mind incontrovertible evidence in support of my diagnosis. His symptoms were almost identical with those of Jolles' patient.

In view of the experiments quoted above, in which so much tin was found in the nervous system, I feel reasonably certain that this man's nervous system suffered severely, and possibly permanently, which accounts for the persistence of his symptoms.

[3] Ungar and Bodlander: Ztschr. f. Hyg., 1887, 11, 241.
[4] Lehman: Arch. f. Hyg., 1902, 45, 88.
[5] Schryver: Jour. Hyg., 1909, 9, 262.

RHINOPHYMA.*

M. G. Seelig, M.D., F.A.C.S.,

St. Louis

Rhinophyma is an essential disease of the nose, of more than ordinary interest. The gross characteristics of the disease and the resultant disfigurement are, in the first instance, striking. From the purely clinical side, the uncertain and possible multiplicity of etiological factors adds interest. From the pathological side there is presented the interesting problem of deciding whether to classify the disease as an inflammatory hypertrophy or as a frank neoplasm, and finally, from the historical point of view, the disease simulates unusual and fascinating interest, owing to the part played by the old masters of classical painting and satire in picturing the disease on canvas and in prints.

From the clinical side, rhinophyma might be described fairly accurately if one merely set down the various descriptive terms which have been used in naming the disease: whiskey nose, pound nose, nodular nose, growing nose, copper nose, elphantiasis of the nose, hypertrophy of the nose, lymphangioma, acne hyperplastica, fibroma molluscum and cyst-adeno-fibroma. In the earliest stage of the disease the nose is a dark copper red, and there are dark red spots about it, particularly on the cheeks and at the glabella. Gradually there appear on the nose lentil-size to pea-size discrete or confluent nodules. As these nodules coalesce, and the soft parts hypertrophy, the whole organ becomes deformed by the tumor-like nodules. The deforming growths occur usually at the tip and on both alæ, and may be discrete and lobulated, or they may fuse, forming one large knob. Sometimes they are pedunculated. Von Bruns reports a case in which the growth reached to the chin, and had to be held aside when the patient partook of food or drink. As a rule, there are only three irregularly rounded lobulated growths situated at tip and alæ, but sometimes there are many small lobes separated by deep furrows. The nodules are usually soft and are coursed by dilated veins, and studded with comedoes and acne pustules. Owing to the activity of the sebaceous glands, the surface of the nose presents an oily varnished appearance, and seems to be pitted by the wide open mouths of these glands. Pressure on the nodules causes macaroni-like plugs of sebum to worm out from the sebaceous glands.

The disease occurs usually in the fifth and sixth decades, that is, the deformity is complete at these periods, the process having taken five to twenty years to develop fully.

There probably is no relationship between the disease and alcoholism. An analysis of the cases shows that there is an infinitesimally small num-

ber, compared with the number of alcoholics; and that many cases of rhinophyma occur in non-drinkers.

The commonly accepted opinion is that rhinophyma, pathologically speaking, represents the terminal stage of acne rosacea that has passed through acne hypertrophica. In many instances the disease seems to rest on a congenital basis; Lassar believed that there was a predisposition to rhinophyma in wide-pored individuals. The essential pathological process is an hyperplasia of the connective tissue of the soft parts of the nose, accompanied by a dilatation of the blood vessels, and hypertrophy or cystic degeneration of the sebaceous glands. The skin follicles show, in places, distinct evidences of suppuration. The openings of follicles and of the ducts of the sebaceous glands are widened, so that they resemble deeply-pitted pores, often giving to the nose the appearance of a sponge. No one has ever satisfactorily
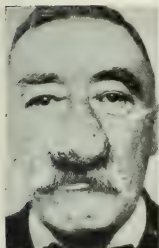

Fig. 1   Fig. 2   Fig. 3   Fig. 4
Fig. 1. Rhinophyma before operation.
Fig. 2. Profile, same patient.
Fig. 3. Same patient after operation.
Fig. 4. Profile, same patient after operation.

demonstrated the cause of the disease. Kaposi sought to prove that the connective-tissue growth, blood-vessel dilatation, and sebaceous-gland degeneration were all secondary to an angioneurosis; but there is no marked consensus of opinion concerning this theory. Trendelenburg considered the disease as a new-growth and grouped it under the head of fibroma molluscum; Lassar considered it a cysto-adeno-fibroma.

I am indebted to Dr. Martin Engman for the privilege of quoting from the advance sheets of his forthcoming book on *Diseases of the Skin*. Dr. Engman from an intensive study of rhinophyma, draws the following conclusions regarding the pathology of the disease: "Rhinophyma is a familial disease representing some type of hereditary transmission. It occurs usually in the seborrhœic type of individual. (The seborrhœic type of Sabouraud may be described as an individual with yellow-tinted, muddy, thick skin, the yellowish tint being most pronounced around seborrhœic areas, with a tendency to acne vulgaris in youth and acne rosacea in middle life.) The

future rhinophyma subject shows a tendency toward flushing of the face, on entering a warm room, after meals, or under excitement. This flushing leads, in time, to a chronic congestion, with secondary chronic infection of the skin of the nose and sometimes of the cheeks. This in turn leads to a chronic productive inflammation, with vascular dilation, connective-tissue formation and dilation of the sebaceous glands into cyst formations. There is a marked thickening of the cutis vera, which throws the skin into folds and furrows. The end-result is the multiple formation of knobs or tumor-like masses."

The treatment of the disease is exclusively operative. The occasional recommendation to practice wedge-shaped incisions should be ignored. The most satisfactory operative procedure consists in shaving off the redundant tissue until the nose is brought back to what one assumes was its original

Fig. 5   Fig. 6   Fig. 7

Fig. 5. Unknown subject, painted by Holbein the younger (1497-1553). Hangs in the Prado of Madrid. (From *Hollaender.*)
Fig. 6. Portrait of supposed grandfather and grandchild of Ghirlandajo (1449-1494). Hangs in the Louvre. (From *Hollaender.*)
Fig. 7. Unknown sitter by a Holland master, in Museum at Stockholm. (From *Hollaender.*)

form. In this shaving process, two things should be borne carefully in mind: (1) do not shave too deeply; and (2) preserve a thin rim of epithelium around the snares. If the shaving is carried too deeply, we remove all sebaceous-gland rests and leave no niduses of epithelium from which, as brood centers, epithelization may spread. This delays healing, and even if the nose be grafted, the resultant skin has a harsh, white, dry appearance so striking as always to command attention and cause comment. Furthermore, deep shaving may injure the nasal cartilages and set up a stubborn perichondritis. If a thin ring of intact skin is not left around the snares, serious disfigurement may result from the contractions incident to cicatrization. Hæmorrhage, which is usually very free, is checked with comparative

ease by simple gauze pressure, and the patient is sent to bed with a large, well vaselined gauze pad over his nose. The next day this pad is removed, and the denuded area is strapped with imbricated strips of sterile zinc oxide adhesive plaster. This plaster dressing is changed daily. Under this simple dressing, my patient, shown in Figures 1 to 4, was completely healed in ten days. It is not necesary to skin graft these patients. Indeed, von Bruns points out that grafting often leads to the development of retention cysts underneath the grafts, with subsequent breaking through and ulceration.

The rôle that rhinophyma plays in medical history and in classical art and caricature is not totally without interest even to a group of practical surgeons. Dr. Eugen Hollaender in his two volumes devoted to *Medicine in Classical Art and Caricature and Satire in Medicine* furnishes some striking copies of pictures that feature rhinophyma.

Fig. 8   Fig. 9   Fig. 10

Fig. 8.   Print of Gerhard Janssen, an old glass etcher of the middle seventeenth century.   (From *Hollaender*.)

Fig. 9.   A caricature from the seventeenth century. One of the so-called Kings of Noses.   (From *Hollaender*.)

Fig. 10.   A caricature of a physician, published about 1700 in Augsburg. (See text for translation of legend.)   (From *Hollaender*.)

Hans Holbein, 1497-1553 (known as Holbein the younger), famous in medical art as the painter of the Dance of Death, painted the portrait of an unknown subject (Fig. 5). The portrait, which hangs in the Prado at Madrid, shows an old man, with a typical rhinophyma, and the characteristic red, congested color scheme which goes with this disease. Hollaender states that the coloring seems to have been toned down by the artist, in order to minimize the existence of the disease as much as possible.

Domenico Ghirlandajo, 1449-1494, the famous Florentine artist, has a picture in the Louvre illustrating rhinophyma even more typically (Fig. 6).

Hollaender's speculations of this particular picture are interesting rather than convincing. He queries as to whether the small tumor on the right brow of the old gentleman may not be intended as a metastasis, thus hinting at the possible belief that rhinophyma was at that time considered to be malignant. Then further, he speculates as to whether the beautiful child's head was intended to soften, by contrast, the jarring asymmetry of the bulbous nose of the old gentleman, or whether the perfect featured little granddaughter was used to disprove the familial nature of the disease.

Hollaender presents these two pictures (Figs. 5 and 6) and the picture by an unknown Holland master (in the museum at Stockholm, Fig. 7) to illustrate the fact that they are pure portraiture, artistically executed without a semblance of caricature. These portraits may stimulate a sense of sympathy but they make no appeal whatsoever to the risible in our make-up.

By contrast, Figure 8 leads away from art, into the field of caricature. This old rhinophyma subject, Gerhard Janssen by name, was a master glass etcher, born in Holland and trained in his art at Dresden, 1650-54. The print itself is not a caricature, but the descriptive phrases engraved about it[1] furnish a caricaturish setting; such phrases, for example, as the legend just above the head, *Nasutus sed acutus* (large nosed but wise) and the sentence in the frame, *Es ist wahr ein unfoermliche Nase, aber sinnreicher Verstand* (a misshapen nose, 'tis true, but talented and wise).

The next two prints are frank caricatures. Figure 9 is from an old seventeenth century pamphlet and is a simon-pure bit of what Hollaender calls naive lack of humor of this period. This king of The Large Nosed stands surrounded by all sorts of impossible things, people, animals, a large horn, a mercury staff, a shepherd's staff, ships, etc., and points proudly to his rhinophymistic organ.

Figure 10 is an even grosser caricature, and represents the tendency at this particular time (late 1600) to use the doctor as a scapegoat and harlequin in jokes and on the stage. This large-nosed doctor, with what might be construed as a rhinophyma knob at the proximal and middle third of his proboscis proclaims:

> "For healthy people, I am a doctor, God help the sick.
> My large headgear embraces profound and numerous thoughts.
> My costume connotes the art that I possess.
> What may be concealed in the urine, my long nose detects."

[1] The legend about the frame is as follows:
A misshapen nose indeed, but a man of talent and wisdom. Art, work and industry bring praise and reward.
The legend underneath the picture is:
Here Gerhard Janssen, former court glass painter, and also experienced in the Damascan art of glass etching. Born in Utrecht, Holland, 1636, July 21; studied at Vreden in Westphalia, from 1650 to 1654. Removed to Vienna in 1662, where he died in 1725, June 3, at the age of eighty-eight years, ten months and eight days. God rest his soul. This print drawn and etched July 25, 1725, by C. D. Metzger, learned in this art, from Speyer, in the Palitinate but at this time residing in Maria Hof, fifteen minutes from Vienna.

And finally, Figure 11 is not without interest from an ethnological point of view. Rhinophyma is fairly common in the American Indian. This is a portrait of Wa-Ha-Gun-Ta, chief of the Chippewas (photographed by Mr. William Burton, of St. Louis, who kindly loaned me this copy). There are authentic records to show that the chief is about 127 years old, and as far as the memory of man runs he has had a typical rhinophyma.

Fig. 11. Chief Wa-Ha-Gun-Ta (American name is Capt. John Smith) of the Chippewas. Still living, and an active hunter in Glacier Park, at an approximate age of 127 years. Rhinophyma is fairly common in American Indians.

ANATOMY AND PATHOLOGY OF THE SEMINAL VESICLES.*

E. O. Smith, M.D.,

Cincinnati.

The seminal vesicles were first described by Fallopius, 1562, and may, therefore, be designated as the male Fallopian tubes. Further analogy between the Fallopian tubes of the female and the seminal vesicles of the male rests on the fact that both are not only frequently involved in inflammatory conditions, but both are often the seat of gonorrheal infection.

Allow me to state here that the basis of this discussion was a prolonged study of many post-mortem specimens of the seminal vesicles, prostates and urinary bladders obtained from the Pathological Institute of the Cincinnati General Hospital.

The seminal vesicles are located between the urinary bladder and the rectum, above or posterior to the prostate gland, and external to the vasa deferentia. The duct from the vas joins a similar tube from the vesicle forming the ejaculatory duct, which with a corresponding structure from the opposite side passes between the posterior and lateral prostatic lobes terminating near the anterior portion of the verumontanum or within the sinus pocularis.

The lower portion of the vesicle rests upon the posterior border of, and is with difficulty separated from, the prostate. This is particularly true if there has been chronic inflammation of these parts. The general direction of the long axis of the vesicle is upward and outward from the posterior border of the prostate for a distance varying from 6 centimeters to 22 centimeters. The angle of divergence varies in different individuals, and may vary greatly in the same individual, this depending upon a collapsed or dilated condition of the urinary bladder. The greater the bladder distension, the farther are the upper poles from the mid-line.

This is an *important fact* to bear in mind when massaging or stripping the vesicles. In many cases where there has been a prolonged obstruction to the outflow of urine from the bladder, the long axis of the vesicles is at almost right angles to the vertical or mid-line of the body.

Except in very short vesicles the upper pole extends to and in most specimens overlaps the ureter where it enters the outer surface of the bladder. The vesicles, except the lowest portion, are external to that part of the outer wall of the bladder which corresponds to the trigone, and are held in contact with this portion of the bladder. This accounts for the vesicle and urinary symptoms that so often accompany vesiculitis and perivesiculitis. It might be added that the aforementioned symptoms have frequently been treated empirically without regard to cause.

The close relation of the upper portion of the vesicle to the ureter explains many cases of *narrowed ureters* due to impingement on the ureter of a pathological vesicle and its consequent thickening, plus the perivesicular inflammatory tissue. All who do cystoscopic work have had the experience of being unable to introduce the ureteral catheter more than three-fourths of an inch to one inch, yet there was urine flowing from the ureter. There can be no doubt but that this failure is often due to a narrowing of the lumen of the ureter and a fixation of it by these external adhesions from the vesicle. As a result of the fixation there is an angulation which the ureteral catheter can not readily pass. It is a well-established fact that a normal kidney may take bacteria from the blood stream
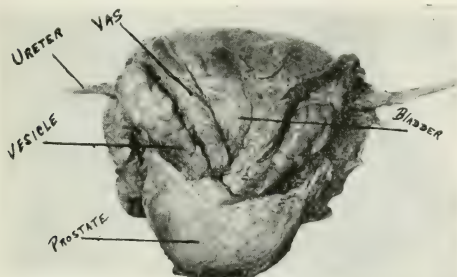

Fig 1. Showing relations of vesicles to prostate, vasa deferentiæ, bladder and ureters.

and deposit them in the urine stream without damage to the kidney itself. It has further been demonstrated that even partial obstruction of the ureter will sufficiently lessen the normal activity and resistance of the kidney so that it becomes easy prey to bacteria in the blood stream.

Following these facts a little further it requires no great strain on the imagination to see how chronic vesiculitis and perivesiculitis can be a predisposing factor in the development of infections of the kidney.

Continuing from the posterior border of the prostate is a *facial membrane* which extends beyond the vesicles. This can easily be separated from the normal vesicle, but with much difficulty where there has been perivesiculitis.

Barnett called attention to the importance of getting beneath this fascia when attempting to expose the vesicles, either for drainage or removal. This line of cleavage once found, the rectum is safe from puncture. Beneath this fascia is found a much thinner fascial layer which envelops the vesicle and ampulla of the vas deferens. Beneath this are other bands of

fascia that hold in place the various loops and saccules of the vesicle. The normal vesicle is easily detached from all its surroundings except at the upper pole, where the blood vessels enter and at the lowest part which is in contact with the prostate. In doing a vesiculectomy the vessels at the upper pole should be ligated *before* removal of the vesicle to prevent troublesome or possible fatal hemorrhage. The loss of blood from a vesiculotomy or simple drainage operation is negligible.

In about one of every ten specimens examined, the *peritoneum* extended well down on the vesicles and occasionally to the posterior border of the prostate. In such cases, one would be dangerously near the peritoneal cavity when operating on the vesicles.
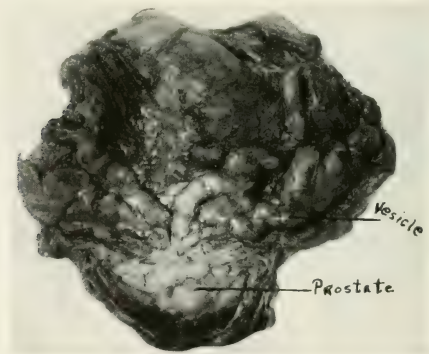

Fig. 2. Long axis of vesicles forms nearly right angles with long axis of body. Upper, outer half of right vesicle contains pus.

One specimen disclosed no distinct vesicles, but mere rudiments about one-half inch in length.

Picker in a paper before the Fourteenth International Medical Congress held in London, 1913, grouped the vesicles according to their anatomical arrangement in five classes: (1) The simple straight tubes; (2) thick twisted tubes with or without diverticula; (3) thin straight or twisted tubes with or without diverticula; (4) straight or twisted main tube with large grape-like diverticula; (5) short main tube with large irregular ramified branches. This seems to be an unnecessary multiplication of classes as the large majority of the specimens I examined were of the continuous tubular type, not twisted but folded at sharp angles upon themselves many times. Most of the other varieties were simple modifications of this type. There

were a few pear-shaped vesicles, whose interior had the appearance of multiple saccules communicating with a common chanel, or vestibule, but not a distinct tube or tubule.

The most *important anatomical feature* of the vesicle from a clinical or pathological viewpoint is the multiple sharp angulations of the tubule in a vast majority of the specimens. There can be no emptying of the vesicles except by some sort of a peristaltic wave which must begin at the blind extremity and travel along the tube towards its outlet into the ejaculatory duct. I am inclined to believe that much of the benefit that patients derive from a properly executed massage of the vesicles is due to a stimulation of this normal peristaltic wave. Very much on the same principle
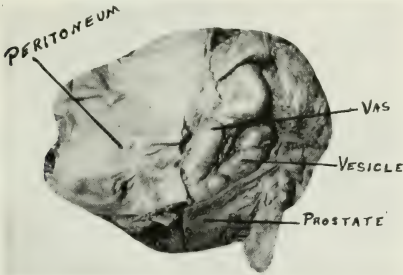

Fig. 3. Peritoneum extends to prostate covering vesicles and vasa. Has been removed from right side

as the old-time massage and kneading of the abdomen to encourage intestinal peristalsis, before the days of Lane's kink, Jackson's membrane and Russian oil. "A properly executed massage," therefore, is a treatment that is not so severe and does not produce trauma.

The appearance of the interior of a normal vesicle is that of fine trabeculations, suggesting irregularly arranged spider webs or tendrils. When this condition does not present and the tubules or saccules are smooth inside, there has been suppuration with destruction of the mucous lining.

The *vesicle wall* is constructed of three layers of tissue. The outer is a fibrous layer, beneath this is a middle layer of muscular tissue, which produces the peristaltic movements that empty the vesicle. The interior is covered with a mucous membrane which probably has some secretory function, not fully and satisfactorily explained. The arrangement of the tubules gives *a very extensive mucous surface with the worst natural drain-*

age. This, partially at least, accounts for the fact that about 50 per cent. of the post-mortem specimens examined were in some way pathological. The farther up the tubule, near the blind end, the more difficult is the drainage, hence we would expect to find most of the pathological conditions in the upper portions of the vesicles, where they are.

Our findings in these specimens demonstrate that a simple single incision, especially in the lower part of a vesicle containing pus, *will* not,

VAS

VESICLE

VESICLE

PROSTATE
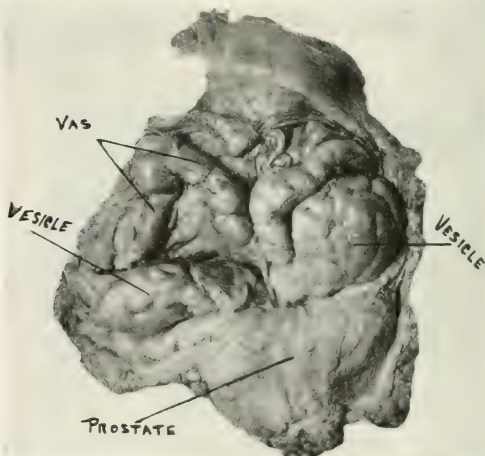
Fig. 4. Vesicles seat of suppuration. Left vesicle turned down showing tortuous and angulated vas.

can not, establish satisfactory surgical drainage. To drain properly, multiple incisions are required, particularly high up on the vesicle. Judging from the specimens alone one would be led to the conclusion that nothing short of a vesiculectomy could be effective, yet we know from practical experience that thorough vesiculotomy is followed by the most satisfactory results in properly selected cases.

While these structures were discovered by Fallopius in the sixteenth century, and recognized as the seat of inflammation by Morgagnii in the eighteenth century (1745), it remained for Fuller and Belfield, about the beginning of the twentieth century, to bring to our attention the importance

of these hollow organs as the hiding place for numerous bacteria—principally Neisser's diplococcus, and its associates, the staphylococcus, the streptococcus and the colon bacillus. It was they who demonstrated the relation between chronic seminal vesiculitis, chronic recurrent urethral discharge, and certain cases of arthritis. Invasion of the vesicles by bacteria from the posterior urethra is certainly a simple matter, there being required only a short trip through the ejaculatory duct, a distance of little more than one inch. Theoretically, at least, one would suppose from the very nearness of the vesicles to the posterior urethra, as compared to the epididymis, that the vesicles would be more frequently involved in secondary infection than in the epididymis. Who can say they are not? It may be that the frequency of vesicular infections varies in direct proportion to the degree of diligence in examining these structures.
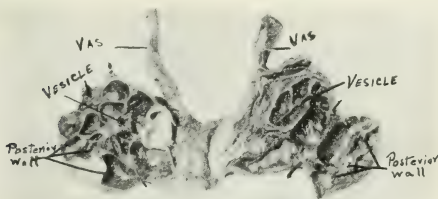

Fig. 5. Vesicles filled with pus, divided in half, posterior walls turned out exposing saccules.

Lewin and Baum examined 1,000 cases of gonorrhea, and found the posterior urethra involved in 65 per cent., and the seminal vesicles in 35 per cent. While there are no statistics at hand to prove the assumption, it seems reasonable that the vesicles could easily be infected from every case of chronic posterior urethritis, and in many cases of acute posterior urethritis. If any surprise is to be expressed, it is that they escape in any case of posterior urethritis.

When looking about for *"focal infections,"* the vesicles must not be overlooked. Before having a few hundred' dollars worth of bridgework removed from a patient's mouth for arthritis, it would do no harm to investigate the vesicles. The fact that the patient states that he has never had gonorrhea should not deter one from examining the vesicles. He may be mistaken or may have forgotten, besides a previous gonorrheal infection is not absolutely necessary.

Vesiculitis may present in men who live under a high nervous tension, who indulge in sexual excesses both normal and abnormal, and who are intemperate in the use of tobacco and alcohol. Horseback riding, bicycle

and motorcycle riding are contributing factors towarl the development of vesicle trouble.

Dr. Robert T. Morris has given out for careful consideration and investigation the suggestion that possibly there is some relation between "focal infection" and malignancy, even though the malignancy be in some part of the body far removed from the focus of infection. While, at first thought, this may seem far-fetched, yet it is a study in biochemistry, which has much more to commend it than the suggestion a few years ago that goitre and mammary malignancy were produced by intestinal stasis.

Tuberculosis of the vesicles is practically always secondary to tuberculosis elsewhere in the genital tract. Contrary to much of the information formerly had, it was found that vesicles which felt nodular when examined digitally per rectum are not necessarily the seat of tuberculosis. What was diagnosed as tuberculous nodules from palpation in some speci-
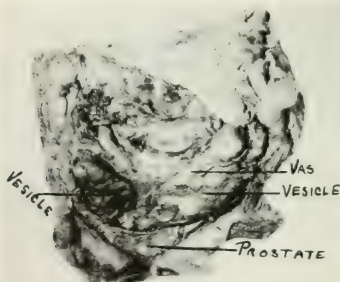
Fig. 6. Dense tissue about vesicles, vasa and prostate, result of chronic inflammation. Left vesicle has been dissected from its bed of adhesions

mens proved to be thickened and sclerosed areas at the sharp angles of the tubules. In one specimen a small single nodule, about the size of a navy bean, was felt in the right seminal vesicle. When this was dissected out it was a very firm and completely capsulated cyst which contained a clear gelatinous material.

The only cases of *malignancy* found were secondary to malignancy in the wall of the urinary bladder. There is no logical reason why the vesicles should not be involved in primary malignancy, and no doubt they are, yet none were found among the specimens forming the basis of this study.

No *calculi* were found in the vesicles among our specimens. They certainly are not very common. Dr. Eugene Fuller informed me in a per-

sonal communication that in the more than seven hundred vesiculotomies that he has performed he found calculi in only seven cases, and but once in both vesicles of the same patient.

There is a case reported by James and Shuman where a seminal vesicle calculus gave rise to the same symptoms as those typical of renal colic, and it was not discovered until after a futile surgical search was made for a stone in the ureter. This is an exceptional case, and an error that anyone might have made. However, with such a case report before us, we should profit by their experience, and ever keep this possibility in mind when studying "renal colic."

The points in the study of the anatomy and pathology of the seminal vesicles that seem worthy of special mention are:

(1)   The wide variations in size and positions of the vesicles.

(2)   Frequency of vesiculitis, both suppurative and inflammatory (focal infections).

(3)   The close relation of the vesicles to the ureters and in some cases to the peritoneum.

(4)   The futility of severe massage treatments.

(5)   The importance of multiple incisions particularly in the distal portions, when surgical drainage is being done.

(6)   Palpable vesicle nodules are not always tuberculous.

BIBLIOGRAPHY

Barnett, C. E.: Pathology of the Seminal Vesicles and Prostate, with Suggestions of the Necessity for Surgical Treatment. (J. Indiana M. Assn., 1909, V. 2, pp. 320-22.)

Barney, J. D.: Observation on the Seminal Vesicles. (Tr. Am. Assn. Genito-Urin. Surg., 1914, V. 9, pp. 72-91.)

Barney, J. D.: Recent Studies in the Pathology of Seminal Vesicles. (Bost. M. and S. J., 1914, V. 171, pp. 59-62.)

Belfield, W. T.: Pus Tubes in the Male, Surgical and Vaccine Treatment. (Jour. A. M. A., 1909, Vol. 53, pp. 2141-43.)

Ceelen, W.: Ein Fibromyom der Samenblase. (Virchow's Arch. f. path. Anat., 1912, V. 207, pp. 206-20c.)

Felix, W.: Zur Anatomie des Ductus Ejaculatorius, der Ampulla Ductus Deferentis und der Vascula seminalis des Erwachsenen Mannes. (Anat. Hefte, 1901, V. 17, pp. 1-50.)

Fuller, Eugene: Seminal Vesiculotomy. (Jour. A. M. A., Vol. 59, pp. 1959-62.)

Hyman, A., and Saunders, A. S.: Chronic Seminal Vesiculitis; A Clinical Résumé with Special Reference to the Urethroscopic Findings in the Posterior Urethra. (N. Y. M. J., 1913, V. 97, pp. 652-654.)

James and Shuman: Seminal Vesical Calculus Simulating Nephrolithiasis. (Surg., Gyn. and Obstet., xvi, 1913.)

Junkerman, C. F.: Hematuria and the Pathology of Chronic Seminal Vesiculitis and Ampullitis Under Which Latter Disorder We Get Bloody Semen. (Med. Century, 1911, V. 18, pp. 113-15.)

Lewin, A., and Bohm, G.: Zur Pathologie der Spermatocystitis Gonorrhoica. (Ztschr. f. Urol., 1909, V. 3, pp. 43-64.)

Nussbaum, M.: Ueber den Bau und die Tatigkeit der Drüsen. VI. Der Bau und die Cyeli-chen Veranderungen der Samenblasen von Ranatusca. (Arch. f. mikr. Anat., 1912, V. 80, 2 Abt., pp. 1-59.)

Oberndorfer, S.: Beitrage zur Anatomie und Pathologie der Samenblasen. (Beitr. z. path Anat. u. z. allg. Path., 1902, V. 31, pp. 325-46.)

Petersen, O. V. C. E.: Beitrage zur Mikrokopschen Anatomie der Vesicula seminalis de Menschen und Einiger Saugetiere. (Anat. Hefte, 1907, V. 34, pp. 237-62.)

Quinby, W. C.: The Anatomy and Physiology of the Seminal Vesicles with Regard to the Treatment of Their Lesions. (Boston M. and S. J., 1914, V. 170, p. 58; discussion, pp. 68-71.)

Thomas, B. A., and Pancoast, H. K.: Observation on the Pathology, Diagnosis and Treatment of Seminal Vesiculitis. (Ann. Surg., 1914, V. 60, pp. 313-18.)

Voelcker (Heidelberg): Die Samenblasen. 1912.

Weisz, F.: Zur Aetiologie und Pathologie der Samenbla-enerkrankungen. (Wien med Press., 1901, V. 45, p. 1581.)

INGUINAL HERNIA.*

THE RELATIVE TEACHING VALUE OF ACTUAL PHOTOGRAPHS AS COMPARED TO DRAWINGS.

CHAS. T. SOUTHER, M.D.,

Cincinnati.

The fact that one book on hernia has forty-two methods describing the operative cure of inguinal hernia and twenty-seven methods describing the cure of femoral hernia, means that many men are either seeking to have their names apply to their operation or there is some fault to find with most, if not all the methods yet devised. I am inclined to believe, after rather extensive study of the subject, that it is a case of "straining at a gnat and swallowing a camel."

Proper application of best known surgical principles to the cure of hernia will result in success and cure of 98 per cent. of the cases.

This paper is based on seven years' careful study of hernia, from text-books, cadavers, that I have seen in large clinics, work among my colleagues and personal operative experience. I was willing very early in my career to concede that scientific operative work for the cure of hernia was much less common than it should be, and that hernia was one of the difficult major operations when considered from all its standpoints.

This is self-evident in the face of the well-established fact that until the last five or ten years recurrence varied from 5 per cent. to 20 per cent. in the hands of various operators, while at present we can hope for 98 per cent. of cures to follow good work.

The student must first have a perfect and complete knowledge of normal anatomy of the hernia region; he must not only be able to tell it, but be able to demonstrate it on both the cadaver and the living subject.

Secondly, he must be able to recognize this same anatomy when the parts are distorted by the pathological conditions found in hernia.

I do not want to undervalue drawings, but want to try to show that more photographs in our text-books would be a great advantage in imparting to students (under and post-graduate) the knowledge necessary for them to have to enable them to do a hernia operation in a scientific, anatomic and curative way.

Any surgical condition that is so common that it can be found in 6 per cent. of the male population and in 2 per cent. of the female population deserves the most careful possible teaching. Further, a very small per cent. of students leaving college are able to do a hernia operation properly, and they usually get less able as they grow older, unless they have hospital training or work as an assistant to some capable surgeon. The simple relief of
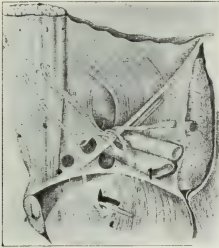
PLATE 1.

Drawings reproduced from Ferguson's Book on Hernia, 1906. Diagrammatic, showing points at which different forms of hernia push through; looking out from within the abdomen.

PLATE 2.

Dissection to show location of incision in aponeurosis of the external oblique, having the external ring intact as a landmark. Cord coming out through external ring. Separation of fibers of external oblique beginning above.

strangulated hernia as an emergency is not saying a man really knew what he did, except to replace the gut.

Incision for hernia includes (1) the incision through the skin, fat and superficial fascia; (2) aponeurosis of external oblique. The direction and location of these two cuts means much. Skin and fat should preferably be lifted up and either cut with scissors or transfixed with a pointed knife, so as not to wound the aponeurosis of the external oblique at a point that is not desirable. The external incision should be located in the folds of the groin and be ample in length. Dr. Wm. Mayo often makes the assertion in his teachings that skin and fat are only coverings, and limited only by

PLATE 3.

Photo of specimen showing cord, deep epigastric vessels, ilio-inguinal nerve and Poupart's ligament.
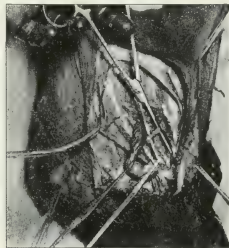
PLATE 4.

Showing knot of suture holding sac; deep epigastric vessels on forceps; ilio-inguinal nerve in grasp of small hemostat over cord at lower end.

PLATE 5.

Showing vas deferens as it passes behind the deep epigastric vessels, internal ring, external ring and muscles.
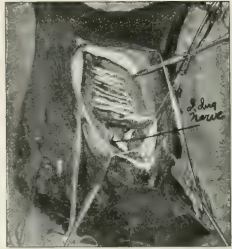
PLATE 6.

Free dissection to show the entire anatomy of hernia; cord reflected inward; deep epigastric vessels show white for contrast. White lines on internal oblique show direction of fibers.

the contents within. In other words, the skin and fat tissues have no retentive or curative influence in the operation for hernia.

The incision in the external oblique muscle or aponeurosis can be made from below up or from above down (Bodine and Judd) and far enough from Poupart's ligament to allow of whatever amount of overlapping may be indicated in the given case. The rule is to divide this aponeurosis half way between Poupart's ligament and the rectus muscle or linear semilunaris; the external ring can be left intact. This overlapping causes the strain to be taken off the internal oblique sutures, and allows more perfect

PLATE 7.

Showing external oblique incision, direction of muscle fibres of internal oblique, sac with neck ligated and being transfixed, cord, deep epigastric vessels and outer pillar of external ring.

PLATE 8.

Ferguson operation, from his book. Stitching cremaster muscle to transversalis fascia. A drawing by Miss Cleveland.

union with the internal oblique and the deeper structures of the canal, meaning cord and transversalis fascia and peritoneum.

Plate 1 is extremely important in enabling the student to diagnose the variety of hernia with which he has to deal, and is probably more illustrative in a way than an actual dissection could be made. It is, therefore, one point in favor of drawings.

Plate 2 shows skin incision of ample proportions, a little larger than necessary, except to get a good photograph. Skin and fat are reflected below Poupart's ligament and above to linea semilunaris, giving full view
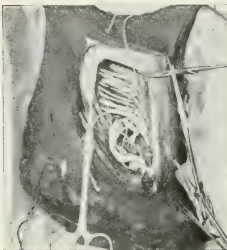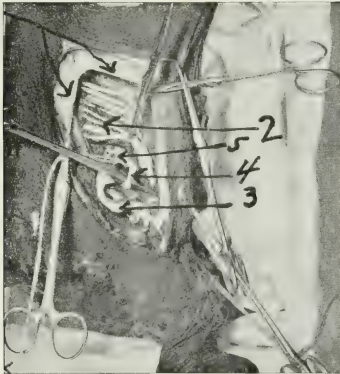

PLATE 9.

Half-tone plate, showing important anatomical structures in hernia: (1) Double arrow, external oblique reflected; (2) internal oblique; (3) cord; (4) deep epigastric vessels; (5) neck of sac ligated, ready to be transfixed. White lines on internal oblique show direction of muscle fibers.

of the entire hernia region and greatly facilitates identification of anatomical structures, making the operation easier and more quickly accomplished. It also shows the location of incision, or rather the point at which the fibers of the aponeurosis of the external oblique are separated, beginning above and going down to the semi-circular fibers that form the external ring. These ring fibers may or may not be cut, or they may be stretched out and nearly or quite obliterated in large scrotal herniæ. In a small hernia don't cut; in large hernia better cut and overlap for support.

If we leave a large leaf in the lower flap of external oblique aponeurosis, we can grasp it with small forceps or rubber-covered clamps, and wipe off (with gauze) the under surface of the aponeurosis and expose (without

PLATE 10.

Continuous suture showing Bassini method, cord brought external to muscle. Author's plate.
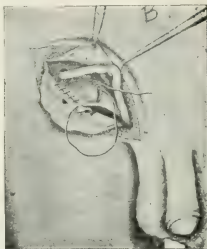
PLATE 11.

Reproduction of drawing from Ferguson's book, showing Bassini operation, with internal oblique stitched to Poupart's ligament; continuous suture used.

effort) the shelving edge of Poupart's ligament, an early and very important step in both the Bassini and Ferguson operations.

This usually takes us down to the cord, and the sac will usually be found (in a small hernia) above and slightly internal to the cord. That is, the sac is next to the conjoined tendon, and the cord is next to the shelving edge of Poupart's ligament, all usually receiving a covering from the cremaster muscle.

Plate 3 shows external oblique reflected, ilio-inguinal nerve passing over forceps lengthwise and cord reflected inward to show location of shelving edge of Poupart's ligament. Passing transversely over the jaws of the forceps are the deep epigastric vessels and sheath ligated. Fibers of external

PLATE 12.

Ferguson's operation, from his book. Reprinted from Ochsner's "Clinical Surgery." Suturing internal oblique to Poupart's ligament. Drawing by A. S. Cleveland.
Page 548
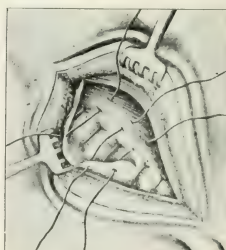
PLATE 13.

Drawing of Ferguson's operation for inguinal hernia in Ferguson's book. Taken from Ochsner's "Clinical Surgery."

PLATE 14.
Continuous suture after Ferguson, holding internal oblique and transversalis over to Poupart's ligament.

PLATE 15.
Suture knot seen in internal oblique is same that ligated and transfixed the neck of the sac. Muscle suture is Ferguson's continuous method.

ring are intact. Internal oblique muscle is here exposed to a greater extent than necessary in operation.

Plate 4. Anatomical, same as Plate 3, with cord reflected down and out, deep vessels up on forceps. Sac of hernia has been ligated and transfixed well up under internal oblique muscle, as shown by knot of thread, which shows well up on surface of internal oblique.

Plate 5. I do not think I have ever seen a plate that demonstrates so perfectly the point at which the vas deferens passes with cord over the deep epigastric vessels. This is important as regards suturing the cremasteric muscle to internal oblique, as advised by Ferguson.

The relative retentive power and influence of the cremaster muscle on the cure of hernia depends on the (1) method of operation and (2) on the

PLATE 16.
First five sutures holding internal oblique and conjoined tendon over to Poupart's ligament, with aponeurosis of external oblique simply approximated.

PLATE 17.
Halstead's operation from Ferguson's book. Sutures tied are holding cremaster muscle under internal oblique.

size or development of the muscle itself. The cremaster forms (with its fascia) one of the coverings of the sac, while it passes through the inguinal canal. By opening this sac and careful preservation of the cremaster it can be used to cover over the cord and attach to the under side of the conjoined tendon and internal oblique (Halstead). In this method it forms the first step in the suture part of the operation.

It is impracticable to use it in a Bassini operation or in cases where the muscle is deficient in development, and has little or no retentive power.

The amount of importance given to this muscle by Halstead and Ferguson and others make us give it a certain definite place in the technique.
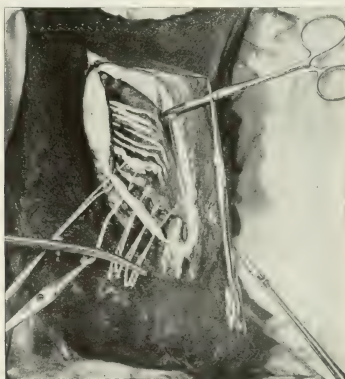
PLATE 18
Half tone photo showing five interrupted sutures passed through internal oblique and conjoined tendon, under shelving edge of Poupart's ligament, with both ends passed through external oblique fascia, so as to tie all knots above external oblique fascia and leave no knots in the canal. Modified Ferguson operation by author.

Plate 6 gives best view of shelving edge of Poupart's ligament, with cord displaced inward.

Plate 7 shows method of ligation and transfixion of the sac, which is believed by a number of authorities to be a very important and essential step in the operation.

Plate 8 is a drawing by a splendid artist and from Ferguson's book. It was unforunate, in the opinion of the writer, to have so splendid a book as Ferguson's work on hernia so profusely illustrated, and not have a single photograph in the entire book.

Plate 8 speaks for itself, and for comparison Plate 10 (my own photo) is intended to illustrate what the real operation looks like.

Plate 9 is the key to all the photos and is intended only to aid the undergraduate student.

Plates 11, 12 and 13 are reproductions of *drawings* from Ferguson's book and are described under each cut.

Plates 16 and 18 are illustrative of what seems to me an advantage in placing the sutures holding the internal oblique (conjoined tendon) over to Poupart's ligament. These sutures are placed as mattress sutures, beginning by passing the round-pointed half curved needle from without through the lower flap of external oblique aponeurosis just above Poupart's ligament, then from without in through internal oblique (conjoined tendon), while the same is held upon finger, then from within, out under Poupart's
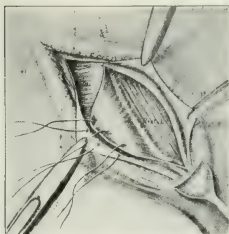
PLATE 19.
Drawing by A. S. Cleveland, after M. Brödel, to show Halstead technique, using the *sheath* of rectus when internal oblique is deficient. From Ferguson's book.

PLATE 20.
Showing three rows of sutures with external oblique fascia overlapped the distance between second and third row of suturing.

ligament, coming out on top of the lower flap of aponeurosis of external oblique fascia.

Overlapping the External Oblique Fascia.—This can always be done, provided the primary incision is properly placed, namely, midway between Poupart's ligament and the linea semilunaris. When the external oblique fascia is overlapped (see Plates 20 and 21), it takes up the surplus in the tissues, and by putting more tension on fascia causes the linea semilunaris to be drawn nearer Poupart's ligament and relieves tension on internal oblique and conjoined tendon, thereby facilitating union of the deeper structures. This carries out the most accepted surgical principles advocated by the best authorities in the treatment of all forms of ventral hernia, namely, overlapping the fascia.

Suture Material.—Consensus of opinion among the big operators is so greatly in favor of animal ligature that wire, silk, linen and silk worm

gut will not be considered. The opinion of Coley, Ferguson, Judd and the late W. T. Bull must be accepted until disproved, and they all use catgut, some chromicized, some plain. Most of them favor a twenty or thirty dry chromic gut, never larger than a No. 2, and Ferguson favors No. 1. Interrupted sutures have the greatest number of advocates.

Three knots should be put on each of the deep sutures, including muscle and Poupart's ligament. For lapping the fascia No. 0 chromic gut may be used. A heavier plain or iodin gut has many advocates.

Never put a tension on sutures, and never tie tight enough to obstruct the blood supply.

Suppuration is constantly present in all wounds where sutures are tied tight enough to stop the blood supply. *Tissues will die when strangled.*
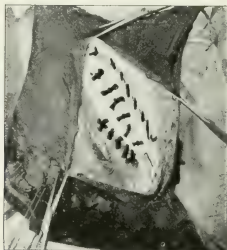
PLATE 21.
Same as previous cut, showing internal oblique and conjoined tendon held by five sutures to Poupart's ligament. Operation complete except for closure of fat and skin; all knots tied above external oblique muscle.

I believe that more returns and more infected wounds in herniæ are due to putting the sutures too tight than all other causes combined. This is particularly true of the skin suture. Some form of non-absorbable suture is best for the skin, but should be removed from fifth to tenth day. However, if there is no tension and tissues are carefully approximated with silk worm gut, silk or linen, either by subcuticular stich or Glover stitch, the suture material will do no harm for ten days. However, the skin suture has done all the good one can hope for in six days, and union will be more rapid if it is removed at this time.

It is claimed by many that a double strand of No. 1 chromic catgut is preferable to a heavier suture material, used single.

The present tendency is all toward the smallest possible ligature that will hold, and No. 1 has been ample for most operators. Personally I have used nothing heavier than No. 2 for any kind of work for years.

In order to tie the knot tightly and not strangulate the tissues, make the first knot easy or loose, and then insert the point of artery clamp under the knot, and tie second and third knot as tight as suture will stand, then remove the forceps, and tissues will not be strangulated.

The writer has favored the antamic operation of Ferguson for several years, but has been perfectly willing to give equal merit to Bassini's method on account of the large number of operators who favor it. Bull and Coley and others are warm advocates of Bassini's method.

If the student will study Coley's and Ferguson's writings, and take the liberty to read a little between the lines, he will see that they do not differ greatly. Coley calls it Bassini's operation with or without transplantation of the cord. Coley's writings have been more especially of hernia in childhood, at which time cure is less difficult.

Disposition of the Sac in Hernia.—Quoting from a recent paper on this subject (C. T. S., *Lancet-Clinic*, October 6, 1909, Deansley, *British Medical Journal*), I believe that effectually removing the sac cures 95 per cent. of cases of hernia.

Macewen lays great stress on complete removal of sac by ligation and transfixion under internal oblique (Plate 7).

Ball (by Ferguson) removes the sac alone in children, and says sutures are not necessary unless cough is present.

Coley says the sac is largely congenital, and its removal is best in all cases.

Ferguson says the congenital deficiency in the internal oblique plays an important part in the etiology, but he always removes the sac.

The consensus of opinion from the recognized authorities on hernia may be taken in abstract as follows: Hernia has a complete sac except in the sliding form, which is rare, but should be borne in mind always.

Removal of the Sac by Suture, Ligature or Obliteration.—Sellenings (*American Journal of Surgery*, March, 1909) claims to have gotten his idea from Matta's treatment of aneurismal sac obliteration. It has been settled beyond a question of doubt that a peritoneal lined sac can be transformed into fibrous connective tissue by proper treatment. Nature proves this by the fact that we all do not have hernial sacs. R. C. Coffee and others have been instrumental in bringing out the clinical proof of same; yet removal and ligation with or without transfixion is the most accepted method today. So important is this care of the sac that in femoral hernia (small variety) removal of the sac with its proper transfixion will cure hernia of the femoral type, even though we do not close the femoral canal (Ochsner).

This same assertion holds good in the treatment of inguinal hernia of early childhood, prior to five years (Ball and E. K. Herring).

The transfixion of the neck of the sac is advocated by Macewen, Butler, Halstead, Ferguson, Lanphear and others; yet in the light of the rôle it

plays in femoral hernia, I do not believe it has been sufficiently emphasized. Treating the stump by this method changes the point of greatest intra-abdominal pressure and greatly facilitates cure. It removes the infundibuliform process of peritoneum and prevents a continuation of the intra-abdominal pressure at this point by obliterating the depression at the internal ring.

The probability of hydrocele developing is greater with Bassini's operation than with Ferguson's. When the distal portion of the sac is left undisturbed, the upper end where it has been severed from the neck should be anchored with small, plain catgut to the cord, and *never ligated*. This prevents formation of hydrocele to a great extent.

My own impression and practice has been to ligate at neck, well up under distal border of internal ring, and cut off. The distal portion of sac may be removed if the hernia is acquired. Distal portion may be left in position when hernia is congenital, that is, when sac is continuous with the tunica vaginalis testis. This point should be determined at once when the sac is opened, and treatment instituted accordingly. The above is subject to some modification when sac is large, thick and old, and it may be treated as individual operator likes.

In further consideration of congenital hernia sac is best treated by Doyen or Bottle's operation for hydrocele. (Recently published as new by E. W. Andrews, Chicago, *Annals of Surgery*, 1909.) Simple eversion around the testicle and one stitch put at the top; this absolutely cures and prevents any possible formation of hydrocele without the time-consuming element of removal.

I always transfix the ligated neck of sac up under internal oblique muscle.

Contents of sac can be returned to abdominal cavity in all simple uncomplicated cases.

Resection of intestine and excision of incarcerated omentum are at times necessary in strangulated forms of hernia, but can not be treated here. A good way to test the re-establishment of the circulation is to replace a doubtful piece of gut into the cavity after having passed a heavy long suture through the mesentery under the gut, so the same gut can be reinspected before closing the hernia. This relief of tension is frequently followed by a return of the color and normal circulation. When the gut can not be replaced without undue pressure it is best to enlarge the ring, or make a second incision above and pull the gut back from within the cavity in femoral hernia.

Charles Harrison Frazier, of Philadelphia (*Annals of Surgery*, October, 1911, p. 555), shows the only cut I have ever seen illustrating the mat-

tress suture for the interal oblique and Poupart's ligament and external aponeurosis which advocates the tying of the sutures all external to external oblique. This was published after the completion of this paper. Rose and Carless "Manual of Surgery," 1907, contains a cut illustrating what Frazier brought out, but no emphasis is put on it in the text.

I have tried to understand what the other fellow has tried to teach, and have tried to present the advantage that the photograph has over the drawing, or at least that it should have a more prominent place in the teaching of hernia than it has formerly occupied.

TOXICITY OF URINE IN PREGNANCY.*

ROBERT W. STEWART, M.D.,

Cincinnati.

In the year 1897 the writer made, with the urine of pregnant women, a number of experiments on rabbits with the object of determining the toxicity of such urine. The great variability in results which Volhard[1] had obtained when going over the work of Ludwig and Savor,[2] Tarnier and Chambrelent,[3] Bouchard[4] and others seemed to justify the conclusion that the intravenous injection into the circulation of so foreign a fluid as urine was open to grave objection, especially as Volhard found numerous cases in which thrombosis was a decided contributing factor, if not the principal one, in the production of death. The writer's experiments were made with urine which had been collected under what was supposed to be careful asepsis, over boric acid. This urine was concentrated, filtered, neutralized and injected warm into the abdominal cavities of rabbits, in the proportion of 80 to 100 c.cm. to kilogramme of animal. The following experiment shows the character of the work done:

"*Experiment VII*—May 13, 1897.—Urine of a primipara (Kramig) aged twenty-one years. Specific gravity, 1,015; acid; no albumin; no sugar. Woman always healthy; well developed; date of expected confinement, June 29, 1897. Family history: Father died of heart disease; mother healthy. No diathetic condition discoverable. This urine was boiled down to one-third of its bulk, to specific gravity, 1,056; fifty cubic centimeters of this concentrated urine were neutralized, filtered, warmed and injected into abdomen of a rabbit weighing 1,750 grammes, in fifteen minutes. 4:00 p. m., returned to cage; can not support himself; lies flat on abdomen; makes effort to regain his feet; respiration slow; supports head against side of cage. 4:07 p. m., has convulsion, tonic followed by clonic spasms, opisthotonos; pupils contracting; breathing in short gasps; lies on side; can not be aroused; palpebral reflex absent. 4:10 p.m., stretches himself every thirty seconds (about); these attacks are undoubtedly convulsive; during interval is quiet. 4:18 p. m., attacks come on regularly and are accompanied by a peculiar grunting sound. 4:24 p. m., the last attack was of longer duration than the others; the abdominal muscles are contracted; the front and hind legs are drawn together; the fore legs tremble while the hind ones move up and down; mouth open; stretching precedes the convulsive attacks, which are becoming more marked. 4:30 p. m., violent convulsion; death.

"Post-mortem examination, eight hours after death; fifty-five cubic centimeters of amber fluid of specific gravity of 1,022 found in abdominal cav-

ity; abdominal vessels injected; organs normal in appearance; post-mortem discoloration of abdominal wall on left side."[5]

The convulsions which are described were found in almost every case, and simulated so closely the convulsions of strychnia poisoning or of puerperal eclampsia that there seemed to be no reasonable doubt that the urine of pregnancy contained deadly poison or poisons, and that the method of injection made no appreciable difference. It seemed further justifiable to conclude that the poison was very soluble, was not affected by heat, and that it was a constant ingredient of the urine, because the mortality was 100 per cent.

During the year 1897, after the results of the foregoing experiments had been published, new experiments were made under the same methods, but upon both rabbits and white mice. The urine was used concentrated and unconcentrated. "The mortality was again nearly 100 per cent. The figures are as follows: Unconcentrated urine taken during the last month of pregnancy killed seven rabbits and two mice, one mouse recovered; when concentrated it killed two mice and failed with one; when taken during labor, unconcentrated urine killed one rabbit and one mouse, and spared none; when taken post-partum, the unconcentrated killed two rabbits and one mouse, and failed with none."[6]

The method seemed good for rabbits and white mice, and no difference could be detected between concentrated and unconcentrated urine. At this juncture, 1898, Dr. F. Forchheimer suggested that we carry on a new line of work, the urine to be taken not only from pregnant women, but also from patients who were suffering from various forms of intestinal auto-intoxication. The results of this joint work were published in the *American Journal of Medical Sciences,* September, 1899. The special work which the writer did in connection with Dr. Forchheimer was published, together with some new experiments, in the *American Journal of Obstetrics,* Vol. XI, No. 3, September, 1899. The mortality in this special work agreed so closely with that in our joint work that the writer can show what that work was by quoting from his own paper.

"The method in detail was as follows: Women were to be near term; the genitals to be thoroughly cleansed with soap and water; the urine to be drawn by sterile catheter into sterile Erlenmyer flasks, which were cotton-stoppered before and after filling; the urine to be immediately boiled and then sent to our laboratory and injected (this was usually done at once, sometimes twelve or more hours later); injections to be made intra-abdominally under same precautions as heretofore, except that the urine was neither neutralized nor filtered. Experiments were made on six rabbits and twelve mice with urine taken from eight women. The proportions used were about the same as those of the previous experiments (80 to 100 cubic centimeters to kilo); a mouse received 25 minims, as a rule, but in four instances 50 minims were injected into these animals. All of the animals

lived except one mouse, which had received 50 minims; it died in twenty-four hours. The mortality was, therefore: Rabbits, nothing; mice, 8 per cent. In addition to these, four other experiments were made on mice with urine taken from women in labor, and one with that of the post-partum period. All of these mice recovered. Three other animals, one rabbit and two mice, received injections of urine which was twenty-four hours old; all died. If these experiments be grouped in classes, it will be found that of urine boiled at once and used within twenty-four hours the figures stand: Seven rabbits and nineteen mice experimented upon, of which six rabbits and sixteen mice recovered, a mortality of rabbits, 15 per cent:; mice, 16 per cent.; all animals together, 15+ per cent. Mortality after urine has stood for twenty-four hours, 100 per cent."[6]

The new experiments to which reference has been made were·made to test this method. As stated in that paper, "I used unconcentrated urine from seven women, the majority of whom were in the last month of pregnancy, the others in the post-partum period. The results show that fresh, unboiled urine killed one mouse out of five, or 20 per cent.; while fresh boiled urine killed two mice out of nine, or 22 per cent.; that the same unboiled urine, after standing for twenty-four hours, in cotton-stoppered, sterile flasks, killed all five of the mice, or 100 per cent.; while boiled urine which had stood for twenty-four hours in similar flasks killed four out of five mice, or 80 per cent."

The experiments of the early part of 1899 agreed with those of Dr. Forchheimer's so closely in regard to mortality that there was good reason to believe that some carelessness in the collection of the urine must have caused the increased mortality in the experiments which are quoted in the preceding paragraph. The writer decided to again test the question, and to include, at Dr. Forchheimer's suggestion, the question of the probable action of bacteria in the production of the poisonous substances which were evidently in the urine. In accordance with this decision and suggestion, a new line of experiments was begun in the early months of 1900. The method was along the lines pursued in the more recent work, but differed not only in the greater care which was used, but also in the particulars which are mentioned below. The details are: The urine was drawn off by means of sterile catheters into sterile cotton-stoppered Erlenmyer flasks at about seven o'clock in the morning, the external genitals of the patient having previously been carefully scrubbed with soap and water, then bathed in lysol solution (dr. 1 to O1), and finally washed off with sterile water. Especial care was given to the meatus urinarius. Stress was laid upon the instruction that the urine was to be the accumulation of the night as nearly as possible. Only one catheterization was permitted, and the urine was drawn off in nearly equal quantities into two flasks, the contents of one of which were to be immediately boiled. The urine was taken from pregnant and puerperal women. This urine was injected intra-ab-

dominally into white mice in quantities of from fifteen to twenty-five minims to the animal. The greatest care was demanded that surgical asepsis be observed in all manipulations. An ordinary hypodermic syringe was used, the needle of which was pointed downwards to avoid wounding liver, heart or other organ. Boiled and unboiled urine was injected into individual mice on the first, second and fourth days, or more definitely within twelve, thirty-six and eighty-four hours of the catheterization. At the time of making the injections, plate cultures were made on gelatin or agar-agar.

Nine series, or forty-eight experiments in all, were made with urine taken from seven women. In seven of the series the urine was taken during the last month of pregnancy, and in two from the post-partum period. The women were all healthy, never showed any symptoms of eclampsia, nor any evidences of kidney or bladder trouble.

Forty-eight mice were used. Forty recovered and eight died. Of the eight, six died after injections of unboiled, and two after boiled urine. The two last-mentioned mice probably died from causes which had nothing to do with any poisonous properties which the urine may have possessed. One died in five days, undoubtedly from asphyxia, as its air supply was cut off by the inadvertent covering of the jar in which the animal was confined; the other died in ten minutes without convulsive action, probably from injury to some organ. These probabilities are strengthened by the fact that unboiled urine from the same catheterization and used at the same time did not kill the mouse. This explanation is made because if these two mice be included in the tables, the mortality rate is 16⅔ per cent. (eight in forty-eight), while if they be excluded, the rate is reduced to 13 per cent. + (six in forty-six). With this explanation it is thought best to include the animals referred to in all subsequent deductions. The details of the mortality are shown in the following tables:

FIRST DAY URINE
(3 to 12 hours)

	Recovered	Died
Unboiled	8	1
Boiled	7	2 (?)

SECOND DAY URINE
(27 to 36 hours)

Unboiled	5	2
Boiled	7	0

FOURTH DAY URINE
(75 to 84 hours)

Unboiled	5	3
Boiled	8	0

If the position which was taken in reference to the two mice that died after injections of boiled urine be tenable, the mortality from boiled urine was nothing, while that from unboiled urine was: First day, 11 per cent.; second day, 28.6 per cent.; fourth day, 37.5 per cent.

It is an interesting fact that in those cases in which the urine was used both before and after delivery, no essential difference was noted, for the reasons that in one case all of the mice recovered, and in the other two mice died from causes not referable to poisonous action, the two to which reference has already been made. Twenty-seven of these mice were used for experimental purposes for the first time, and twenty-one had been used before. Of the former, twenty-four recovered and three died; of the latter, sixteen recovered and five died. Two of the fresh mice should not be included for reasons already stated, a fact which makes the mortality in fresh mice one in twenty-five, or 4 per cent., while that of mice which were used more than once was five in twenty-one, or nearly 24 per cent. This fact would seem to be conclusive that repeated injections did not produce immunity, did not lessen the susceptibility.

<div align="center">CULTURES</div>

The following table shows the number of cultures made, the day upon which they were made, kind of urine used, and whether the culture was made upon gelatin or agar-agar.[1]

<div align="center">FIRST DAY</div>

	Gelatin	Agar-Agar
Unboiled	6	3
Boiled	6	3

<div align="center">SECOND DAY</div>

	Gelatin	Agar-Agar
Unboiled	4	3
Boiled	4	3

<div align="center">FOURTH DAY</div>

	Gelatin	Agar-Agar
Unboiled	4	3
Boiled	5	3

These cultures were examined in twenty-four and forty-eight hours. The presence or absence of growths is shown in the following tables:

<div align="center">NO GROWTHS IN TWENTY-FOUR HOURS</div>

<div align="center">FIRST DAY</div>

	Gelatin	Agar-Agar
Unboiled	6	0
Boiled	6	2

[1] Attention is called to the fact that these cultures were made at the time of making the injections; that is, the first day represented the time from three to twelve hours after drawing the urine, the second day from twenty-seven to thirty-six hours, and the fourth day from seventy-five to eighty-four hours.

SECOND DAY

	Gelatin	Agar-Agar
Unboiled	4	2
Boiled	4	3

FOURTH DAY

Unboiled	4	1
Boiled	5	2

GROWTHS IN TWENTY-FOUR HOURS

FIRST DAY

Unboiled	0	3
Boiled	0	1

SECOND DAY

Unboiled	0	0
Boiled	0	0

FOURTH DAY

Unboiled	0	2
Boiled	0	1

NO GROWTHS IN FORTY-EIGHT HOURS

FIRST DAY

Unboiled	4	0
Boiled	5	1

SECOND DAY

Unboiled	4	2
Boiled	4	3

FOURTH DAY

Unboiled	3	1
Boiled	4	2

GROWTHS IN FORTY-EIGHT HOURS

FIRST DAY

Unboiled	2	3
Boiled	1	1

SECOND DAY

Unboiled	1	0
Boiled	0	0

FOURTH DAY

Unboiled	1	2
Boiled	1	1

It will be seen that of the twenty-nine cultures which were made upon gelatin, all were sterile in twenty-four hours, and twenty-four showed no growths even in forty-eight hours, while of the eighteen cultures made upon agar-agar, ten were sterile in twenty-four hours, and nine showed no growths in forty-eight hours. Whether this greater disposition on the part of the latter substance to develop colonies was due to faulty preparation or to its being a better culture medium, can not be determined by anything in this work. The probabilities are that there was less care exercised in drawing the urine which was used in these series than in the gelatin series, because of the six deaths which were fairly attributable to poison in the urine, four occurred in the agar-agar series. This receives some confirmation from the fact that in the agar-agar series, boiled and unboiled urine showed a nearly equal proclivity to the development of colonies, whereas in that series in which gelatin was used unboiled urine showed a much greater tendency to the development of colonies than did the boiled urine.

No difference in the development of colonies could be discovered between the urine taken ante-partum and that taken post-partum, but not much stress can be laid on this fact, as there were but two patients whose urine was so taken.

<div align="center">CAUSE OF DEATH</div>

A careful post-mortem examination, which included the blood, was made upon each mouse. The following table shows number of case, amount of urine injected, cause of death, whether urine was unboiled or boiled, from which day urine was taken, sterility or infection of urine at time of death, and time in which death occurred:

1	15 minims	Inanition	Boiled	First Day	Sterile.	5 days
2	24 minims	Septicemia	Unboiled	Fourth Day	Sterile.	36 hours
3	20 minims	Injury (?)	Boiled	First Day	Sterile.	10 min.
4	25 minims	Septicemia	Unboiled	First Day	Numerous colonies	
5	25 minims	Septicemia	Unboiled	Second Day	Sterile 24 hours; numerous colonies 3rd day	17 hours 12 hours
6	20 minims	Septicemia	Unboiled	Fourth Day	"Loaded" in 24 hours.	12 hours
7	25 minims	Septicemia	Unboiled	Second Day	Loaded in 48 hours.	18 hours
8	20 minims	Septicemia	Unboiled	Fourth Day	Loaded in 24 hours	24 hours

The first three specimens were from the same patient. Nos. 1 and 2 was taken nine days before delivery, and No. 3 twelve hours after delivery.

The next three specimens were all taken about six weeks before delivery from the same patient. Two control experiments were made from urine taken from the same patient at the same time, but which was not used until the fourth day. Both mice recovered, although the unboiled urine showed two hundred (?) colonies and the boiled urine was sterile.

The last two specimens were taken from same patient less than four weeks before delivery.

In not one of these mice was there any macroscopic evidence of peritonitis or injury to the abdominal organs. In Nos. 1 and 3 nothing was found microscopically in the blood. These are the mice whose deaths were attributed to inanition and injury, respectively, as has already been explained. In No. 2 rather large bacilli were found in the blood; in No. 4 small ovoid bacilli were present; in Nos. 5 and 6 the bacilli were large; in Nos. 7 and 8 diplococci were found.

Unboiled urine was injected in all those cases of death in which septicemia was diagnosed, or in which micro-organisms were found in the blood, and it, therefore, is a fact of considerable significance that the boiled urine, which was drawn at the same time as the unboiled, and which was injected at the same time, did not kill in a single instance.

As far as could be ascertained none of these mice had convulsions before death. This is largely surmise, however, because in most cases the animals were found dead. In the few cases in which the death struggle was observed no convulsions occurred.

If all this work be taken in review it will be seen that urine collected—that is, passed by patient over boric acid—evidently contains a convulsive poison which is deadly in 100 per cent. of the cases, to rabbits and white mice, whether the urine be concentrated or unconcentrated; that when the urine is drawn by catheter under strict surgical asepsis, the mortality is greatly reduced, and that when the urine is so drawn and immediately boiled the mortality is practically nothing. This contrast at once suggests the possibility of error in the deductions which have been drawn by investigators who have used the boric acid method, a method which has undoubtedly been followed when the urine is sent from any distance, or has been allowed to stand two, three or four days before use for experimental purposes.

Even in the writer's work asepsis plays the important rôle, because in the early part of 1899 the manipulations were made practically under his supervision, and the mortality was reduced to 16 per cent., while in the latter part of the same year the drawing of the urine was not done by his own assistants, consequently could not be so carefully supervised, and the mortality rose to much greater proportions. The experiments of 1900 were again under his direct care and the mortality fell again to the figures of the early part of 1899. Forchheimer's individual work confirms this statement.

The relation of mortality to sterility or infection of the urine at the time of the death of the animal is very interesting.

The table shows that two specimens of boiled urine which were sterile at time of injection and remained sterile afterwards, killed mice—the two which have been excepted throughout these tables; two specimens of fresh urine showed no growths in twenty-four hours, but developed numerous colonies in the succeedings days; three specimens of fresh urine were contaminated within twenty-four hours, and one in forty-eight hours. In other words, all of the fresh urine which killed mice must have contained micro-

organisms at the time of the injection, and in every case septicemia or the presence of bacilli could be demonstrated in the blood. It is reasonable to suppose that these organisms either existed in the blood of the mothers, in their bladders, or were introduced into the urine during the manipulations. The women were all healthy, had no fever, nor other systemic disturbances, no anorexia nor local deviation from the normal, and consequently could not have had blood so saturated with bacilli as to infect the urine. The absence of epithelium, albumin, blood and pus cells and the freedom from pain on urination, prove there was no cystitis. As the source of the contamination there is left, then, only the manipulations. This position is strengthened by the fact that the septicemia could not have been due to the presence in the blood of these animals of bacilli which only became virulent because of the injection, for the simple reason that numerous other animals had been kept in the cages with the ones which died, had gone through the same process of experimentation and yet recovered. Therefore, it seems to the writer that any other view of the cause of death than infection of the urine at the time of catheterization or during some of the subsequent manipulations would be illogical and strained.

Not that the writer means to imply that imperfect oxygenation of food or tissue metamorphosis, with consequent production of uric acid, carbonic acid, paraxanthin and the xanthin bodies generally, may not mean the poisoning of the system, as has been claimed by so many distinguished authorities. Nor is he willing to say that these substances are not thrown out of the system by the kidneys. Above all, he does not wish to be understood as claiming that bacteria are the sole cause of death in the animals which have been used by other experimenters.

At the same time one can not deny that, as far as the present work goes, there is good reason for believing that what has heretofore been attributed to poisons generated in the human body was often due to micro-organisms which must have been introduced into the urine after it was voided. The one claim which Forchheimer and the writer do make is that the methods, and consequently the deductions of the other experimenters, are open to serious objection, and that the intra-abdominal injection of urine which has been drawn by catheter under strict asepsis is freer from objection than the intravenous method.

Finally, while the writer is diffident in claiming too much for the effect which bacteria may produce in this line of work, it is a significant fact that in his own cases 75 per cent. of the deaths can not be attributed to any other cause than bacteria.

Note—Dr. Allan Ramsey did the bacteriological part of this work and materially assisted in all of it. He deserves the credit and has my gratitude.

LITERATURE.
1 Vidhard, M. castellz t Geb. n Gyn., Bd V, 1896.
2 Ludwig, n. Savor, Monatschr. f. Geb. u Gyn., Bd. 1, 1896.
3 Larnert et Chamberlant. Soc. f. Biol., 1892, No. 44.
4 Bumhard, "Auto-Intoxication."
5 Stewart, Amer. J. Obst., 1896, Vol. XXX, No. 3
6 Stewart, Amer. J. Obst., 1899, Vol. XL, No. 3

THE EARLY DIAGNOSIS OF SYPHILIS AND A COMPARATIVE STANDARDIZATION OF THE TREATMENT.*

E. B. TAUBER, M.D.,

Cincinnati.

In the problem of syphilis it is imperative to secure an earlier and more efficient diagnosis of the disease than is the case at the present and a more generalized effective treatment. This should be the keynote of our endeavors.

The early diagnosis of syphilis is an unknown quantity to many men who are practicing medicine in our times. To men who have the older ideas of the disease to guide them, ideas that are firmly planted in their minds by a couple of decades of practice, it seems almost sacrilege to insist that waiting for secondaries is a criminal action and that we lose the benefit of the one psychologic moment in the life history of syphilis when we can seize our real opportunity.

The definite diagnosis in the early primary stage before the spirochete has spread to the lymphatic system near the primary lesion and before the serologic reaction is positive is the one and only time that, taken advantage of, may lead to success, and it is the time for action instant and effective. This is the time for radical cure if such is possible. An injection of arsphenamin here can put an immediate end to infectivity of the case. A sterilization complete and entire seems possible here. The suppression of the biologic and serologic evidence of the disease is possible and may be probable here. This should be our treatment for paresis, tabes dorsalis, iritis, etc.

PROPHYLAXIS OR TREATMENT THAT WILL PREVENT THESE CONDITIONS

The first week or so of the initial lesion, while syphilis is still a local condition, is the time that we should employ every energy and endeavor of our diagnostic and therapeutic armamentarium to cure, for never again in the picture of syphilis for the individual patient or the state will this moment return.

Our public health services, medical colleges, hospitals and clinics must teach this point and ever impress it on all in contact with them; that is, the student groups, the nursing groups and the public in general, these facts and necessities.

The dark field examination must be a routine at the clinics, in the hospitals and in our private practice. The organism must be known and recognized by all.

The newer staining methods, such as the Medalia method, must be taught generally. There can be no valid objection to teaching the profession of the future and the present the only means of diagnosis for the period when the dangerous sequelæ may be mastered and dominated by us.

Every sore, whether on the genitalia or elsewhere, is or should be open to a suspicion of chancre and should be repeatedly examined for *Spirochaeta pallida*. Every papule, nodule, crack, excoriation and herpetic or other erosion should be viewed with the possibility of an initial lesion and should be examined for *Spirochaeta pallida*. Chancroids should not be accepted as uncomplicated with syphilis; double infection is always possible.

Antiseptics applied, especially mercurials, make the finding of *Spirochaeta pallida* difficult or almost impossible, and because of this we should teach that no mercurial dressings, or better still, no antiseptics, should be applied to any lesions until the examination for *Spirochaeta pallida* has been made, and if any have been used, it should be made a routine to irrigate thoroughly with physiologic sodium chlorid solution and to apply a wet dressing of the solution for twelve hours or more before examining for *Spirochaeta pallida*. To obtain *Spirochaeta pallida*, a definite method is important. We have used in the Cincinnati General Hospital this method:

The surface of the lesion is wiped with a cotton sponge to remove superficial organisms. The wound may be rubbed or teased lightly, but one should not cause bleeding; just an oozing that will give serum to transfer to a new clean side and slip should be produced. Immersion oil is put on both the under surface of the slide and upper surface of the cover. This will give a continuous airless medium from dark field to objective. A focus with fine adjustment should be secured until one gets a dark background with the glistening moving particles in white rings. Then a search for the twisting spirochetes may be instituted.

As a professional body, let us be honest and acknowledge that we have not spread the vital importance of early diagnosis. It has taken a world war to impress on us that the modern conceptions of syphilis have not been taught in our medical colleges. We have zealously striven to whitewash the episodes occurring in the wrecks due to this disease. We have had clinical characteristics and endless discussions as to secondaries and tertiaries and neurosyphilis, forgetting that we were proving our guilt in this very manner, and now we must scrap our clinical differences and turn to laboratory diagnosis to the finding of *Spirochaeta pallida*. I do not mean here the serologic diagnosis, for then we are losing our great opportunity.

TRAINING THE PROFESSION TO EARLY DIAGNOSIS

How can we create this? This is our tremendous duty. You must all aid this. We must aid all the men who will do dark-field work in the

smaller towns and villages and show them and others by our support that we are back of them. The internists, the surgeons of the smaller localities must call on the man in that locality who has special knowledge of syphilis, and this will cause the demand to be supplied. We must send to Coventry the man who cauterizes or applies some medicament to the sore on the penis or other location before advice, and competent advice at that, is given and the dark-field tests are made.

In early syphilis, systematic treatment must be immediate and must be pushed vigorously; sledge-hammer treatment here is indicated, not feather-duster types of treatment. Syphilographers will doubtless agree that the effective time for arsphenamin is early, before the serologic tests are positive. So, then, this places on us the burden of outlining a method or scheme for treatment that shall be more or less standardized. Here I mean a treatment for the majority of cases, not for individual ones; also a treatment that will not be inflexible but one that has been tried over a long period of time in a sufficient number of cases to at least have the merit of being successful. The outline I wish to submit has been tried at the Cincinnati General Hospital, the outpatient dispensary, the night venereal clinic and in my private practice, all of which I have under my control, and our results have been very good. Our method is as follows:

A SUCCESSFUL METHOD OF TREATMENT

Courses of from four to six intravenous injections of arsphenamin of from 0.3 to 0.6 gm. at intervals of from three to seven days are given, combined with mercury. Here we may with one or two such courses effect a cure. But even with such vigorous treatment a second or third course of arsphenamin of the same type is advisable after a two months' interval, given with the same courses of mercury.

In all cases, after the Wassermann test is positive, I believe at least three such courses of both arsphenamin and mercury to be the minimum, and more can be given as indicated. I believe that mercury, given either by intramuscular injections of soluble or insoluble preparations or by rubs, is of great aid to our arsphenamin therapy, and in the rational cure of syphilis, mercury and arsphenamin must be combined.

The courses of mercury should be from ten to twelve injections, at weekly intervals, of an insoluble; or from twenty-four to thirty, given every other day, of a soluble, or thirty to forty daily inunctions. I myself believe in giving one course of each type of mercury with each course of arsphenamin. Serologic tests should be made once a month at first, and later at two month intervals, until the test seems to become permanently negative as shown by at least five unbroken negative tests, each six months apart, with no treatment and no clinical evidence of syphilis before we should become in the least optimistic in regard to the case as being checked or cured.

It is my opinion that provocative injections and spinal puncture with the colloidal gold test may be made; but there is a difference of opinion as to this need, except in cases that require these special methods.

In late syphilis, mercury and iodids should be pushed in courses with arsphenamin given in the same way.

In secondary syphilis, the first year, three courses as above outlined of from six to eight doses of arsphenamin in each course, combined with mercury, and not less than three of such courses are indicated.

The second year, if the Wassermann test remains positive or there is recurrence of any lesion, practically a repetition of the first year's treatment, as outlined, will be necessary.

If the Wassermann test is negative and remains negative and there is no recurrence of lesions, at least four doses of arsphenamin in conjunction with two courses of mercury are recommended.

The third year, if the Wassermann test remains negative and there have been no recurrences from the first year, a patient should pass into a period of observation with regular periods for a serologic examination. If there is any nerve involvement or tabes and paresis, the treatment will depend on the individual case and will be cavered by any general methods; but treatment must be pushed for years.

Congenital or hereditary syphilis requires longer and more persistent treatment; but again more individual treatment is necessary and cannot be outlined in the same way that early acquired syphilis can be. To recapitulate, my outline is as follows as regards standardization for early syphilis:

Arsphenamin and mercury to be given combined.

Arsphenamin, each course from four to six doses of from 0.3 to 0.6 gm. intravenously at three to seven day intervals.

Mercury (insoluble), gray oil, mercuric salicylate, twelve doses at weekly intervals, dose from three to five minims.

Mercury (soluble), twenty-four to thirty injections of mercuric cyanid or mercuric chlorid, given every other day.

Rubs, twenty-four to thirty given every day.

First Year.—First course of treatment, from two to two and one-half months. Rest, one month. Second course of treatment, from two to two and one-half months. Rest, two months. Third course, from two to two and one-half months.

Second Year.—If Wassermann is negative, rest after third course for four months; mercury, two months; rest, four months; mercury, two months.

If Wassermann is positive, rest, two months; course of arsphenamin and mercury, two months; rest, two months; arsphenamin and mercury, two months; rest, two months; arsphenamin and mercury, two months.

Third Year.—If Wassermann is negative, patient passes to period of observation with regular serologic examinations.

If Wassermann is positive, rest after last course, two months; arsphenamin and mercury, two months; rest, two months; mercury course, two months; rest, two months; arsphenamin and mercury, two months, and so on, being controlled by serologic findings.

It is not easy to state when a cure is accomplished; but, in general, we can only say, by intensive therapy safety can be secured and in most cases a cure can be effected. This may result in overtreating in some cases, but it is better to err in this way than to undertreat a single one, and some cures require a definite amount of treatment on a definite basis, if the needed results are to be obtained. Therefore, before patients are told they are well, even after repeated negative Wassermann tests without treatment (for negative Wassermann tests during treatment only indicate that progress is being made), I consider it necessary that at least two or three years of negative serologic tests without treatment or recurrence of any symptoms indicative of syphilis shall elapse before we can even say that we think the pathologic condition is eliminated. In so brief a paper I could cover only majority cases, and no attempt has been made as regards treatment or outline for individual cases.

CONCLUSIONS

1. No single sign of improvement should be accepted as definite or final, and treatment should not be stopped at such indication. Only cessation of all around symptoms is indicative, and that only if it continues through years.

2. Arsphenamin therapy is necessary, since it controls infectivity and contagion. It yields quick results.

3. Mercury is essential but as a splint to our arsenic therapy and as an aid to permanence in cure.

4. Most syphilis is undertreated. Sledge-hammer blows are indicated. Overtreatment is to be preferred to undertreatment.

5. It is better to be overconservative rather than optimistic in stating that a cure has been effected. Our modern therapy is still in too infantile a stage to justify anything but overconservatism.

I believe that specializing and efficiency tendencies can be obtained, and very ably, in the treatment of syphilis.

Hospitals and clinical centers in our larger cities can be used by smaller centers. The extension of war-time methods in the army to civil practice will and should come.

In a few words, I believe syphilis is as easily preventable as other infectious diseases. With syphilis an actual condition, it must be recognized

early and treated early if its economic results are to be prevented. Thus our problem is early recognition and early treatment. The early period is its period of greatest transmission; also the period in which our chances of curing a patient are greatest. This places the burden squarely where it belongs, on us, the medical profession, and also on the public health service, medical schools, hospitals and clinics. These different agencies must individually disseminate knowledge, acquire competent teachers, and adequate equipment to give adequate treatment and to graduate competent physicians. This means that syphilis needs centralization, efficiency, control, and the teaching of the early diagnosis of syphilis and a comparative standardization of its treatment.

INHALATION EXPERIMENTS ON INFLUENZA AND PNEUMONIA, AND ON THE IMPORTANCE OF SPRAY-BORNE BACTERIA IN RESPIRATORY INFECTIONS.*

WILLIAM B. WHERRY AND C. T. BUTTERFIELD.

Cincinnati.

While the influenza virus appeared to be of reduced virulence during the outbreak of February and March, 1920, the occasional occurrence of a family outbreak, or of rapid death due to pulmonary edema, seemed to indicate that it was identical with that present in the outbreak of 1919. We feel particularly sure that we were dealing with cases of influenza in the family of S., because the mother, father and eight children all came into the hospital at once. Most of these ten patients had bronchopneumonia and one purulent pleuritis. Cases R. and S., B. and B. and T. were of a milder type, although B. and T. had secondary bronchopneumonia. These cases were chosen because most of them had been ill for only a day or two at the time the material was collected.

Thirty-eight cases, including those just cited, were examined bacteriologically. All aerobic, partial tension and anaerobic blood cultures were negative. For the throat and sputum cultures we used + 0.5 agar containing 5 per cent. of rabbit blood. Incubation was at 37 C. under aerobic, partial tension and anaerobic conditions. B. influenzae was isolated from twelve cases. Six of the twelve were from the family S., who all became ill at once. From the father of this family we failed to isolate B. influenzae, and he was ill for months with streptococcus empyema. In six cases B. influenzae was the predominating organism and in four it was present in pure culture.

When B. influenzae was grown at partial tension it retained its minute bipolar form and showed less tendency to involution than when grown aerobically. All the strains were strictly hemoglobinophilic while the Koch-Weeks bacillus was isolated on aerobic, partial tension and anaerobic slants of ascites agar, and could be subcultured on this medium. All strains failed to produce indol in hemoglobin broth when the sulphuric acid-sodium nitrate test was applied. However, the growth in our broth was scanty. Most of the associated bacteria belonged to the pneumococcus, hemolytic streptococcus and staphylococcus groups. No colonies that might have represented the B. enteritidis (type M 5), which appeared in the sprayed animals, were noted, and it is not likely that they were overlooked, for M 5 colonies on blood-agar plates at partial tension are a vivid green—as are those of typhoid, paratyphoid B. and B. enteritidis.

Antigens from all strains tested were prepared at one time and kept under the same conditions. Cultures were washed and suspended in 0.9% salt solution, killed at 65 C. for thirty minutes, freed of clumps and preserved with 0.5% phenol.

Agglutinating serum for B. influenzae and the Koch-Weeks bacillus were prepared by inoculating rabbits with living cultures. In the case of M 5 a dead antigen was necessary. The serums had a rather low titer, about 1:800.

TABLE 1

AGGLUTINATION AND ABSORPTION REACTIONS

		Mother Antiserum		Koch-Weeks Antiserum	
Designation of Strains		Simple Agglutination	Homologous Agglutinins Absorbed	Simple Agglutination	Homologous Agglutinins Absorbed
1	Mother	.		. .	
2	B.	.	.	- -	
3	H.		P	+	P
4	S.	+	+		
5	M				
6	S	.		. .	
7	C	.	P	-	
8	A			. .	
9	Sam	-		- -	
10	K	-		- -	
11	Leo	.		- -	
12	Koch-Weeks			+	+

+ means positive agglutination.
- means no agglutination.
P means homologous agglutinins.
P means homologous agglutinins only partially absorbed. When simple agglutination tests were negative absorption tests were not made.

As shown in Table 1, four of the strains from the family S., mother, B., S. and M., and strain C from a healthy individual, are probably identical. One other of the family strains, H., is somewhat related to this group, but is about as closely related to the Koch-Weeks bacillus. This agrees with the work of others in showing that there are distinct serologic groups among the influenza bacilli and that some strains are closely related to the Koch-Weeks bacillus.

Blood serum from some of the recovered members of family S., who had harbored B. influenzae, contained no agglutinins for this organism.

ATTEMPTS TO TRANSMIT INFLUENZA TO WHITE MICE AND RATS, GUINEA PIGS AND RABBITS BY MEANS OF SPRAYED SPUTUM

Sputum, or, when this could not be obtained, material swabbed from the tonsillar area, but generally both, were thoroughly shaken with 0.9 per cent. salt solution and sprayed by means of a Vilbiss atomizer within half an hour after collection. The animals were placed in a metal box about 12 x 10 x 6 inches, provided with a glass window and air outlets. The spraying was continued until the chamber was filled with vapor. This was repeated at intervals until 15-20 c.c. had been sprayed. After from 30-60 minutes the animals were removed from the cage and each series kept in separate cages. These were scalded with hot water before they were used for any given series. The sawdust bedding was not sterilized. Precautions were taken to sterilize the drinking pans in the case of all mouse experi-

ments. The animals were fed on cracked maize and vegetable waste from the hospital kitchen.

It might be noted here that one of us in Cincinnati inoculated sterile milk with influenza sputum (1919) and incubated it at 37, 24 and 15 degrees for from 1-14 days, and fed it to white rats and white mice. Of about forty animals so fed only two mice died, one with pneumococcus septicemia, and one with pneumonia and serous pleuritis due to four different bacteria. None of these bacteria, singly or combined, produced infection when fed to other mice in milk or broth cultures.

Table 2 gives the data on these experiments.

TABLE 2
INFLUENZA SPUTUM SPRAYING EXPERIMENT

Date	Material Used to Infect Source	Method of Exposure	Number and Species of Animals Exposed	Number of Animals Fatally Infected	No. of Infected Animals with Pneumonia	Minimum and Maximum Duration of Illness, Days	Percentage of Fatalities	Remarks
2/ 3/20	Sputum S	Spray	5 mice	4 (1 killed)	(M1, M2)	19-73	80	All like M5
2/ 3/20	Sputum S	Spray	4 white rats	2	2 (W1, W2)	13	50	Sterile
2/ 3/20	Sputum S	Spray	2 guinea-pigs	2	1 (G.-P.-3)	8-80	100	Like M5
2/22/20	Lung emul-sion M1	Intraperi-toneal	2 mice	2	0	6-8	100	General infec-tion like M5
2/23/20	Mixed culture M1 plate	Spray	2 mice	2		8-12	100	M6 like M5
3/ 3/20	Lung emul-sion M5	Spray	2 mice	1	1 (M5, M6)	12	50	Like M5
2/25/20	Organ emul-sion M1	Spray	2 mice	0	0	..	0	
2/16/20	Organ emul-sion W1, W2	Intraperi-toneal	2 white rats	0	0		0	
4/23/20	Organ emul-sion G.P.3	Spray	2 mice	1	0	40	50	
3/23/20	Organ emul-sion G.P.3	Spray	2 guinea-pigs	1	0	30	50	General infec-tion like M5
2/ 4/20	Sputum cul-tures case S	Spray	6 mice	2	2	31-45	33	No growth ob-tained from any tissue
2/ 4/20	Sputum cul-tures case S	Spray	2 guinea-pigs	0	0	.	0	Killed and found nor-mal 5/2/20
2/ 4/20	Sputum cul-tures case S	Spray	2 white rats	0	0	..	0	
2/ 4/20	Sputum cul-tures case S	Spray	1 rabbit	1	1 (R1)	8	100	Gt coccus present, lung large num-bers
2/16/20	Culture R1	Intraven-ously, intraperi-toneal	2 rabbits	2	2	34-40	100	Infecting agent not R
3/ 2/20	Sputum R and S	Spray	2 mice	2	1	33-45	100	Like M5
2/ 2/20	Sputum R and S	Spray	1 guinea-pig	1	1	26	100	Like M5
3/ 3/20	Sputum R and E	Spray	8 mice	4	1	30-38	50	Like M5, one sterile
4/ 4/20	Lung emulsion R and E 30-day mouse	Intraperi-toneal	2 mice	1	1	50		Like M5
4/ 7/20	Lung emulsion R and E 38-day mouse	Intraperi-toneal	1 mouse	1	0	3	100	Like M5
3/ 5/20	Sputum R and E	Spray	6 mice	1	0	52	.	Like M5 from lungs
3/ 5/20	Sputum T	Spray	6 mice	2	0	7-54	33	Like M5

Family S, Sputum Spray: Four of five mice died infected with a strain of B. enteritidis (type M 5): two of these died of a primary pneumonia due to M 5. By the term primary pneumonia we mean pneumonia without marked involvement of the liver and spleen, which invariably occurs in a general infection, *i. e.*, after feeding.

Of two guinea-pigs, one died of primary pneumonia due to M 5. One of two mice and one of two guinea-pigs sprayed with extreats of the spleen, liver and lungs of this animal died of general infection with M 5.

Two of four rats died of primary pneumonia and the long cultures yielded no growth, nor were subinoculations of organ extracts fatal to rats.

Partial tension rabbit blood-agar plate cultures, from the sputum used for spraying the animals, were sprayed after twenty-four hours' growth at 37 degrees Of six mice, two guinea-pigs and one rabbit, only three mice died—two mice the 31st and 45th day were sterile bacteriologically, and one rabbit of primary pneumonia, apparently due to a gram-posiive coccus, which, however, did not appear in the two subinoculated rabbits.

R. and S. Sputum Spray.—The two mice sprayed died of infection with M 5, one of primary pneumonia. The guinea-pig died of primary pneumonia due to M 5.

B. and S. Sputum of 3/2.—Of eight mice, four died, but only one of these had pneumonia due to M 5. Two had general infection due to M 5.

B. and B. Sputum of 3/5.—Of six mice sprayed one died on the 52nd day of general infection with M 5. The rest, which were killed three months later, were found to be normal and did not harbor M 5.

Sputum T.—Of six mice sprayed, two died on the 72nd and 84th days thereafter; one had a general infection with M 5. The remaining four were killed three months later and found to be normal.

Summary.—That animals sprayed with influenza sputum comprised thirty-three white mice, of which four died of primary pneumonia and nine of a general infection with M 5. Of this same lot of mice, six were sprayed with culture material and of these two, which died, were sterile on bacteriologic examination; two were killed and cultured two months later and found to be uninfected, and two were used for another experiment in which they survied for a month.

Of five guinea-pigs, two died of primary pneumonia; the lungs of these animals contained numerous B. enteritidis, which were culturally and serologically identical (agglutination and absorption) with M 5.

Of six white rats similarly exposed, two died of a primary pneumonia due to an unrecognized cause and not transmissible to rats by intraperitoneal inoculation.

The work of Krumwiede, Valentine and Kohn[1] shows that these animals may develop spontaneous infection with members of the paratyphoid-enteritidis group. We did not encounter a single death among our unused stock due to such bacteria, nor were we able to isolate such bacteria from the intestinal tract, liver, spleen and lungs of six normal mice. However, the experiments detailed in Table 7 show that a certain number of mice which are intoxicated by killed cultures of M 5 or by the sterile Berkefeld filtrate of broth cultures, develop a secondary infection with M 5. In such endogenous infections, following intoxication, pneumonia occurred only twice in forty animals.

Furthermore, of twenty-nine mice sprayed with a virulent culture of the pneumococcus, only one died of infection with M 5, and this mouse had received a previous dose of M 5 toxin. On the other hand, as shown in

[1] Jour. Med. Res., 1918, 38, 1, 29.

Table 5, mice exposed to sprayed cultures of M 5 almost invariably died of a primary pneumonia.

In the light of these data one is tempted to believe that the animals developing infection with M 5 were injured in some way by something in the influenza sputum. Nevertheless, the possibility of purely spontaneous infection exists and the question can only be settled by further work with more adequate controls, *i. e.*, an equal number of animals from each lot used for an experiment should have been kept under identical conditions as controls.

INOCULATION OF OTHER ANIMALS

From one of the typical cases, "R," 20 c.c. of blood was obtained. This was used to inoculate a series of animals not generally used in laboratory experiments with the hope that a susceptible animal might be encountered. These were a pig, eight weeks old, weighing about 100 pounds, a ferret, an opossum, a salamander, and a black-headed nun. None showed any abnormal symptoms during three months' observation.

THE CULTURAL AND AGGLUTINATIVE RELATIONSHIP OF M 5 (TABLES 3 AND 4)

Since all the enteritidis-like organisms isolated from the mice and guinea-pigs exposed to sputum sprays corresponded in their agglutination, absorption and cultural characteristics, we used M 5 alone for the comparative study. Unfortunately only two antiserums, M 5, with a titer of 1:800, and paratyphoid B., with a titer of 1:10,000, were available. Table 3 shows that M 5 is entirely distinct from paratyphoid B., but that it is indistinguishable by this test alone from Danysz virus and from B. enteritidis. However, the cultural results (table 4) show that Danysz virus agrees with paratyphoid B. in its failure to ferment xylose, while M 5 agrees with B. enteritidis in the fermentation of this substance. This divergence was brought out by Krumweide et al.[3] We have been helped also in this study by reference to the work of Jordan,[4] and preceding articles cited here and that of Winslow, Kligler and Rothberg.[5] The Danysz virus and paratyphoid B. were from the U. S. Hygienic Laboratory and the B. enteritidis was of the Gaertner type and came from Prof. E. O. Jordan in 1901.

Five cultures of B. enteritidis-like organisms isolated from the stools of influenza patients by Sherwood, Downs and McNaught,[6] were sent by Dr. Sherwood. None of these agglutinated with M 5 antiserum.

EXPERIMENTS SHOWING THAT BROTH CULTURES OF M 5 CONTAIN A SOLUBLE TOXIN WITH WHICH AN ANTITOXIN MAY BE PRODUCED

Plain maltose and dextrose beef infusion broths were tried. It was found that 0.1% dextrose broth (+0.05) yielded the most potent toxin. After incubation at 37 C. for 4-5 days the culture was filtered through a Berkefeld N. The filtrate would kill mice in 12-18 hours when 0.05-0.1 c.c. was injected intraperitoneally. Seventy mice were used in establishing the nature and potency of this toxin. Mice dying of intoxication showed marked injection of the subcutis and congestion of the lungs. Often the

TABLE 3

SIMPLE AGGLUTINATION OF CERTAIN STRAINS BY B. PARATYPH. B. AND M. 5 ANTISERUM AND THE ABSORPTION OF HOMOLOGOUS AGGLUTININS FROM THE SAME

Designation of Strains	Para B. Antiserum		M 5 Antiserum	
	Simple Agglutination	Homologous Agglutinins Absorbed	Simple Agglutination	Homologous Agglutinins Absorbed
M 5				
Para B....				
Enteritidis .				
Danysz virus... .				

[3] Jour. Med. Res., 1919, 39, p. 449.
[4] Jour. Infect. Dis., 1920, 26, p. 427.
[5] Jour. Bacteriol., 1919, 4, p. 429.
[6] Jour. Infect. Dis., 1920, 26, p. 16.

pulmonary congestion bordered on consolidation. The lungs often showed numerous capillary hemorrhages. Other organs and tissues appeared normal to the eye.

We found that about 2 c.c. was the M. L. D. on intravenous inoculation, for a rabbit weighing 1,800 gm. By inoculation with sublethal doses and gradually increasing the amount at two-day intervals, over a period of three weeks, a rabbit could tolerate 5 c.c. of a freshly prepared toxin. Eight days after the last dose of toxin the serum of this rabbit would protect mice when mixed with 2 M L D of the toxin and at once inoculated intraperitoneally.

In the experiments summarized in Table 7 the vaccine was prepared by suspending an agar culture in 0.9% salt solution, heating at 65 C. for sixty minutes and preserving with 0.5% carbolic acid. The density was somewhat greater than that of a 24-hour broth culture of B. typhosus. The dosage was approximately two minims for each inoculation. Several tests of the vaccine before and after its use showed that the bacilli were dead.

TABLE 4

THE MORPHOLOGICAL AND CULTURAL CHARACTERISTICS OF M. 5 AND OF REPRESENTATIVE ORGANISMS SELECTED FROM THE SAME GROUP

	Gram Stain	Motility	Litmus Milk Initial Acid	Litmus Milk Final Strongly Alkaline	Indol	H2S Produced	Gelatin Liquefied	Voges Proskauer	Endo's Acid	Green Colonies Bacteria Typhosus Blood Agar Plates	Dextrose	Maltose	Galactose	Saccharose	Levulose	Lactose	Mannite	Adonose	Dulcite	Erythrite	Isodulcite	Mannose	Raffinose	Salacin	Xylose
M 5											ag	ag ag		ag	ag ag ag		ag ag		ag ag	— ag
Donysz virus											ag	ag ag	ag	ag ag ag		ag ag		ag ag	—
B. Prar. II											ag	ag ag	ag	ag ag ag		ag ag		ag ag	
Enteritidis											ag	ag ag	ag	ag ag ag		ag ag		ag ag	— ag

ag = acid and gas

TABLE 5

EXPERIMENTS SHOWING THAT WHEN ANIMALS ARE EXPOSED TO THE SPRAY OF M 5 CULTURES A LARGE PERCENTAGE DEVELOP PNEUMONIA, AND THAT SIMILAR RESULTS FOLLOW THE SPRAY OF DONYSZ VIRUS, WHILE A SPRAY OF B. INFLUENZA ISOLATED 48 HOURS PREVIOUSLY FROM AN INFLUENZA LUNG WAS WITHOUT EFFECT

Date	Animals	Number of Deaths	Percentage Dead Animals with Primary Pneumonia	Duration of Illness in Days	Remarks
3/14/20	4 mice	4	100	4-20	
3/17/20	10 mice	8	100	4-15	
3/30/20	4 mice	4	75	1-10	Sublethal dose M 5 toxin given few hours before spray. One toxin death
3/25/20	5 mice	4	100	4-12	
4/ 8/20	1 mouse	1		16	
4/11/20	2 guinea pigs				
5/ 5/20	4 mice	4	100	12-20	Donysz virus spray B. influenzae

TABLE 6

LATE MICE's SHOWING FAILURE OF IMMUNIZE AGAINST M 5 CULTURE SPRAY BY PREVIOUS INOCULATION WITH SUBLETHAL DOSES OF M 5 SOLUBLE TOXIN

Date	Number of Mice	Number of Deaths	Duration of Illness in Days	Remarks
4/6/20	4	3	11-16	One dose soluble toxin 6 days before spray
4/6/20	5	4	15	Four doses soluble toxin at 3 day intervals. Last dose 2 days before exposure to spray
4/6/20	3		14	Controls without toxin

TABLE 7

Experiments Showing Failure to Immunize Against M 5 Spray by Previous Subcutaneous
Inoculation with a Killed Culture

Date	Number of Mice	Number of Deaths	Percentage of Dead Animals with Primary Pneumonia	Duration of Illness in Days	Remarks
5/7/20	4	4	100	12-23	One dose 10 days before exposure to spray
5/7/20	4	3	33*	1*- 8	Two doses at 4 day intervals. Last dose 10 days before spray
5/7/20	4	3	66.*	8-14	Three doses at 4 days intervals. Last dose 10 days before spray
5/7/20	5	5	80	6-14	Controls not vaccinated

* Two mice died of general infection with M 5 before the time for exposure to the spray.

Experiments Showing that Primary Pneumonia Is Not Produced in Mice When
M 5 Is Inoculated by Other Means Than Spray

When the portal of entry was through the conjunctiva, the buccal and gastro-intestinal mucosa, the subcutis or peritoneal cavity, general infection followed. In two cases there was a secondary pneumonia. In such cases the liver and spleen were greatly enlarged and full of whitish necrotic or proliferative areas. These organic lesions are not present in mice dying of inhalation pneumonia. Placing the culture on the nasal mucosa was without effect.

The mice fed M 5 were kept without food and water for from 1-2 days and then each one was watched while it lapped up the drops of a 24-hour broth culture. Those fed heavily ate bread soaked with the broth culture.

TABLE 8

Experiments Showing that Primary Pneumonia Is Not Produced in Mice when M 5 is
Inoculated by Other Means than Spray

Date	Method of Inoculation	Number of Mice	Number of Deaths	Percentage with Pneumonia	Duration of Illness in Days	Remarks
3/18/20	Fed heavily	4	3	0	6-14	General infection
3/31/20	Intraperitoneal	4	4	0	2-4	General infection
4/20/20	Fed 1 drop	4	1	0	8	General infection
4/20/20	Fed 5 drops	4	3	0	10-18	General infection
4/20/20	Fed heavily	2	2	50	8-9	General infection, one secondary pneumonia
4/20/20	Fed heavily	2	2	0	12-17	General infection
5/11/20	Subcutaneous	3	3	0	2-5	General infection
5/11/20	Ocular conjunctiva	3	2	33	9-19	General infection, one secondary pneumonia
5/11/20	Anterior nares	4	0			

Experiments Showing That Sprayed Bacteria Are Actually Inhaled Into the
Deepest Parts of the Lungs

(a) Four mice and one guinea-pig were sprayed with a broth culture of M 5, and chloroformed within thirty minutes from the beginning of the experiment. They were wet with alcohol and immersed in 1:1,000 bichlorid of mercury for five minutes. Then they were dissected with aseptic precautions and from each animal 4-6 small pieces of the lungs (1-3 mm. in diameter) were snipped off with sterile scissors and planted in broth. In every instance all the pieces yielded growth of M 5 within twenty-four hours. Many of the pieces of lung represented the extreme distal portions of the anterior and posterior lobes. Five normal mice controls were treated in the same way. All cultures from these remained sterile during 72-hours' observation.

(b) Experiment (a) was duplicated except that a very virulent pneumococcus (type I) was used and the tissue was planted in glucose rabbit blood broth. The four mice were killed and cultured as in experiment (a) at two, four, eight and eighteen hour intervals after the spray. In every instance the cultures showed that pneumococci were present in the deepest parts of the lungs. Cultures from one control mouse yielded no growth in the same medium.

ATTEMPTS TO PRODUCE PNEUMONIA IN MICE BY SPRAYING PNEUMOCOCCI

Having shown that sprayed bacteria reach the deepest alveoli, or capillary bronchi, of the lungs and that pneumococci planted in this way survive in the lungs of mice for at least eighteen hours, the maximum period tested, we made the following experiments with a type 1 pneumococcus. This culture had been kept highly virulent for mice at the United States Hygienic Laboratory.

Four mice were sprayed with the growth from four blood agar slants suspended in broth. They were exposed for thirty minutes. Two died of primary lobar pneumonia in fourteen days. No bacteria could be found in the purulent exudate and all cultures remained sterile. The remaining two were killed six weeks later. They appeared normal and cultures from the lungs remained sterile.

The mice were kept at 8 C. for four hours and then sprayed. They felt warm on removal from the icebox. Two were killed and cultured shortly after spraying. Pneumococci grew out of all pieces of their lungs, including the most distal portions. At the end of four weeks the remaining eight mice were chloroformed and cultured with negative results.

Since M 5 soluble toxin injures the lungs of mice, six mice which had survived sublethal doses of this toxin given ten days before were sprayed. They were killed six weeks later and found normal. Nor did they harbor pneumococci.

Four mice were given sublethal doses of M 5 toxin and sprayed with pneumococci at once. Six weeks later one of these mice died of pneumonia caused by M 5; no pneumococci could be found. The remaining three were killed and cultured eight weeks later. They were normal and the cultures remained sterile.

Three mice were sprayed with the pneumococcus and then in an attempt to give them an acidosis they were kept under ether for one hour. One of these was further chilled in ice water for ten minutes. They survived and yielded no growths four weeks later.

Two mice were sprayed with a broth suspension of bloody sputum from a case of pneumococcus lobar pneumonia. They remained well during six weeks' observation.

Since none of the twenty-nine mice became infected after inhaling virulent pneumococci into their lungs, one may conclude that some predisposing factor must precede or accompany such an implantation of bacteria. While we owe the whole idea of droplet infection to Flügge and his pupils and confess that we have relied on the review of their work by Goetschlich,[6] we are not aware of the fact if these workers demonstrated that bacteria are to be recovered from the deepest portions of the lungs of sprayed animals. Our attention was drawn to this by Rogers,[7] who showed that tubercle bacilli could be recovered from the lungs of guinea-pigs immediately after spraying them with tuberculous sputum, and that such protected and sprayed animals develop true primary pulmonary tuberculosis.

We are familiar with the work of Dürck,[8] who, by means of intratracheal insufflation, was unable to infect the lungs of rabbits with freshly isolated cultures of pneumococcus, streptococcus pyogenes, and staphylococcus aureus unless at the same time, or before or after, injurious dust particles, pumice, or "Thomasphosphatmehl" were also blown into the lungs. This sterile dust alone produced pneumonia while sterile street dust did not. He also describes the production of typical pneumonia in rabbits, with secondary invasion of the pneumonic areas by B. coli, sarcinae,, or Friedländer's bacillus, by keeping them at 37-41 C. for sixteen to thirty-six hours and then in ice water for two to seven minutes.

Handbuch d. path. Mikroorg., Kolle und Wassermann, 1914, Vol. 2
Amer. Rev. Tuberc., 1919, 3, p. 48, and 1920, 3, p. 784.
[8] Deut. Arch. f. klin. Med., 1897, 58, p. 368.

However, these experiments and those made by the method of intra-bronchial insufflation, which was introduced by Lamar and Meltzer and used by many others, do not appeal to us as represnting what must take place under natural conditions. Bacteria can be inhaled into the deepest parts of the lungs and if they are capable of multiplying there they will produce pneumonia, as in the case of M 5. The fact that virulent pneumococci do not multiply when planted in the lungs of mice by air currents is an interesting fact and deserves further investigation.

SUMMARY AND CONCLUSIONS

When white mice, white rats and guinea-pigs were exposed to finely divided influenza sputum sprays some died of a primary pneumonia, others of a general infection due to a strain of B. enteritidis (type M 5). Since the work of others has shown that these animals may die of spontaneous infection with members of the paratyphoid-enteritidis group we can not say that these infections were necessarily the sequel to the spray. However, as primary pneumonia could not be produced in mice when M 5 was inoculated through the buccal or gastro-intestinal mucosa, the conjunctiva, subcutis or peritoneal cavity, but only when sprayed, it seems to us likely that something in the sputum sprays produced a change in the pulmonary tissues favoring such secondary localization.

Broth cultures of M 5 contain a soluble toxin which produces marked congestion of the subcutaneous and pulmonary tissues of white mice. This toxin gives rise to an antitoxin when injected into rabbits. Previous inoculation with the toxin did not produce immunity to the development of primary pneumonia by sprayed cultures, nor were we able to immunize against the spray of M 5 cultures by previous subcutaneous inoculations with a dead culture.

The intoxication of mice with the soluble toxin or with killed cultures of M 5 apparently led to infection with M 5 in a small percentage of the used mice. We were not able to find this bacterium in normal mice, nor did spraying mice with virulent pneumococci make it show itself as a secondary invader.

Experiments show that M 5 and virulent pneumococci are inhaled by mice into the deepest alveoli or capillary bronchi of the lungs, and that primary pneumonia follows in the case of M 5, which is capable of growing and producing its toxins there, whereas the virulent pneumococci gradually disappear.

THE PRINCIPLES OF TREATMENT IN MERCURIC CHLORID POISONING

WITH RESULTS OF TREATMENT*

H. B. Weiss, M.D.,

Cincinnati.

Within the past two years there has been much work done in the various phases of mercuric chlorid poisoning. Before then, most of the work reported was of a therapeutic nature; but recently new and important laboratory data have been contributed. These new data have certainly put the modern therapeutic measures to the test, discrediting many and placing a few on a firm basis.

The anatomic pathology has been well established. Every organ of the body is affected, the liver and kidneys bearing the brunt of the injuries. From a cloudy swelling the changes continue to fatty degeneration and necrosis. When the poisoning is severe, hemorrhagic inflammation may supervene.

Schamberg, Kolner and Raiziss,[1] in their studies of the comparative toxicity of the various preparations of mercury used for therapeutic purposes, have shown in a long series of dogs that every animal develops evidences of nephritis of varying degrees after injections of both the soluble and insoluble mercury salts. The nephritis produced is primarily tubular, with frequent accompanying glomerulonephritis (hemorrhagic) in the severer instances. The changes in the tubular epithelium they attribute to a direct toxic degeneration of the cells by the mercury, and not to an inflammatory reaction depending on the elimination of toxic substances.

Mercury has been obtained from the blood of dogs within ten minutes after its administration by mouth.[2] Burmeister and McNally have shown that the kidney changes vary with the size of the dose in massive intoxication, and that the liver changes depend on the duration of the intoxication.

The important newer studies consider the question from a chemical standpoint. It is from this point of view that the present treatment must be evolved.

As the mercury is quickly taken up by the blood after ingestion, it is evident that all the tissues are quickly bathed with the toxic material. In a fatal case of mercury poisoning, it was found that almost one-third of the mercury recoverable from the body was obtained from the blood.[3] In 1916,

Lewis and Rivers[4] found that the retention of waste nitrogen was a factor in the production of early fatalities. More recently MacNider,[5] in an exhaustive study, has demonstrated some essential facts. Those animals that did not succumb from the early gastro-enteritis developed a severe type of acid intoxication, as evidenced by the production of acetone bodies, the reduction of the alkali reserve of the blood, and the increase in carbon dioxid content. Constantly associated with this acid intoxication was a kidney injury. He states that delayed kidney injury is not due to the action of the mercury as such during its elimination by this organ. He[6] had previously shown that acetone and diacetic acid are developed in nephritis produced by uranium, and that administration of alkaline carbonates lessened the
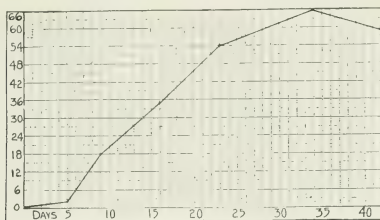
Percentage of phenolsulphonephthalein output after a patient who developed anuria for three days began to void.

toxicity of the uranium and delayed the formation of the acid bodies. Furthermore, when the kidney was protected by carbonate, it was found that the kidney remained functionally more active, and that there was a diminished acute swelling, fatty degeneration and necrosis of the renal epithelium.

It is this work which has proved correct the therapeutic principles that I have employed in the treatment of mercuric chlorid poisoning.[7]

The symptoms of poisoning by mercury are well known: locally burns, and later vomiting and gastro-intestinal hemorrhages; as the toxemia progresses, oliguria, then anuria and finally "uremic" symptoms, as convulsions and death.

Many remedies, empiric and allegedly scientific, have been advocated in the use of mercury poisoning, but they seem not to have stood the test

[4] Lewis, D. S., and Rivers, T. M.: Chemical Studies on a Case of Bichloride Poisoning. Johns Hopkins Hos. Bull., 1916, 27, 183.
[5] MacNider, W. de B.: A Study of Acute Mercuric Chlorid Intoxication in the Dog with Special Reference to the Kidney Injury. Jour. Exper. Med., 1918, 27, 519.
[6] MacNider, W. de B.: The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate. Jour. Exper. Med., 1916, 23, 171-187.
[7] Weiss, H. B.: A Method of Treatment of Mercuric Chlorid Poisoning, The Journal A. M. A., June 2, 1917, p. 1618; The Treatment of Bichlorid of Mercury Poisoning, Ohio State Med. Jour., 1917, 13, 597.

of time. We have used the alkaline treatment for more than three years, and our records show a lower mortality than that ordinarily reported.

The principle involved in the use of alkali is that of trying to counteract the acid intoxication produced, which in turn produces the generalized toxemic swelling and degeneration of all the body tissues.[8] When there is present oliguria, with blood and casts in the urine, we have evidences of acute kidney injury. This discernible kidney injury is merely an indication of an injury common to all the body tissues, for we know that the entire organism has been bathed by the mercury. The alkali is not given as an eliminant, but to counteract acid intoxication, edema and cloudy swelling, which, if permitted to go on, proceed to fatty degeneration and irreversible cell damage (necrosis).

Sansum,[9] in a recent paper, seems to believe that the basis for the use of alkali is to be found in its power to increase diuresis with a secondary washing out (increased elimination) of mercury. Because he finds no increased mercury elimination, he leads his readers to suppose that the use of alkali as a therapeutic agent is valueless. The alkali, however, is not used solely for its eliminatory action, but to inhibit and to counteract damage to the tissues which mercury, if left to itself, produces.

At present we can report on fifty-four consecutive cases of mercurial poisoning with but three deaths. Of the three patients that died, two received the treatment only after unavoidable delay, and one had a pre-existing nephritis and cirrhosis.

METHOD OF TREATMENT

Essentially the treatment which I have proposed consists of an early washing out of the mercury salt from the stomach and intestine and continued introduction of sufficient alkali to overcome the acid intoxication.

The patient should come under observation as early as possible, for I have found that when the treatment is delayed for any reason, the symptoms produced by the mercury poisoning become more difficult to control. Two patients of my series died, I think, because treatment was commenced too late.

I usually wash out the stomach with a mixture of one quart of milk and the whites of three eggs, following this by a saturated solution of sodium bicarbonate until the stomach washings return clear. Finally, before the stomach tube is removed, from three to four ounces of crystallized magnesium sulphate dissolved in from six to eight ounces of water are allowed to remain in the stomach. A soap suds enema is then given.

Usually the patient vomits shortly after taking the mercury, thereby aiding in the elimination of the poison.

The next step is to introduce alkali, and we give the alkali by mouth, rectum and intravenously. As soon as possible after washing the stomach,

[8] Fischer, M. H.: Edema and Nephritis, New York, John Wiley & Sons, 1915.
[9] Sansum, W. D.: The Principles of Treatment in Mercuric Chloride Poisoning, The Journal A. M. A., March 23, 1918, p. 824.

the patient is given Fischer's solution intravenously. Fischer's solution consists of crystallized sodium carbonate, 10 gm. (Na_2CO_3 10H_2O) (or 4.2 gm. of the ordinary "dry" salt); sodium chlorid, 15 gm., and distilled water, 1,000 c.c.

Depending on the state of the circulatory system, from 1,000 to 2,000 c.c. of the solution are given intravenously as a first dose. We continue the alkaline medication by giving eight ounces of "imperial drink" every two hours. This drink consists of: potassium bitartrate (cream of tartar), 4 gm. (one teaspoonful); sodium citrate, 2 gm. (one-half teaspoonful); sugar, 2 gm. (one-half teaspoonful), and water, 240 c.c. (eight ounces).

This drink is flavored with lemon or orange juice. The patient is allowed large quantities of it.

There is no restriction in diet at any time during the treatment.

As an indication of the severity of the acid intoxication, and as a guide to the amount of alkali and salt that needs to be given, we use the analysis of the urine. Except in suppression cases (which were rare in our series), the patient voids large quantities of urine, the amounts depending on the amount of fluid taken. The urine should become alkaline to methyl red (a saturated solution of methyl red in alcohol) and be kept so, for Fischer has demonstrated that if the urine of a nephritic can not be maintained alkaline to methyl red, the patient continues in a serious state. If the output of urine is not seen to be maintained, and if its reaction does not become alkaline to methyl red after the first intravenous injection, a second intravenous injection is given the following day, and general alkali administration by mouth or rectum is continued.

RESULTS

Under this treatment, there is usually produced and maintained a free secretion of urine which remains alkaline, and an output of albumin in the urine, which usually develops early, rapidly disappears. Ordinarily two intravenous injections of the alkali, together with the solution of potassium bitartrate and sodium citrate, which is given at hourly or two hourly intervals, day and night (when the patient is not asleep) has been found sufficient to keep the urine alkaline and to keep the output of urine normal. The blood and casts in the urine are usually quickly dissipated. The patient is kept under observation for about ten days after the urine has become normal, and is then discharged.

I have shown previously[10] that patients treated early show fewer symptoms and make a more rapid recovery than those in whom treatment is delayed.

We have performed phenolsulphonephthalein tests on most of our patients, and it is interesting to note that those who were treated early showed only slight or no diminution in phenolsulphonephthalein output. When the output was diminished, it rapidly rose to normal and continued so. In one patient who developed an anuria for three days,[10] the phenolsulphonephthalein output was practically zero for five days after he commenced to void, and then rapidly rose to 66 per cent. (as shown in the accompanying chart) at the end of thirty-three days. This patient's urine was normal six months after his recovery from the mercuric chlorid poisoning.

[10] Weiss, H. B. (footnote 7, *loc. referentur*).

THE VENEREAL PROBLEM.

PHILIP ZENNER, A.M., M.D.,

Cincinnati.

My subject is the venereal problem; that is, the problem of the prevention of the venereal disease. This is no new problem. Many years ago, a great American surgeon expressed the fear that these diseases would lead to the deterioration of the whole human race.

Have these diseases been on the increase as this fear suggests? We have no data which enable us to give a definite answer to this question, but there is much which gives that appearance.

When I was a student, paresis and locomotor ataxia (I suppose that you know that they are due to syphilis) were rarely found. Today we see them frequently. But we know much more about these diseases than we did in those days, and, therefore, more readily recognize them, and this may be the full explanation of their apparent greater frequency.

Then we have a new test of syphilis, a blood test—the Wassermann test—which enables us to find the disease in many cases where it would otherwise have gone unrecognized. We have also a new test for gonorrhea, so that now we know that gonorrhea is common in women and children, of which fact we were not formerly aware. In women the disease often leads to confirmed invalidism and is a common cause of sterility; in children it often causes blindness.

These facts do not prove that venereal diseases are on the increase, but they have aroused the world to a knowledge of their prevalence and their danger. The problem became acute when we entered the war.

War always has increased the venereal diseases. They spread rapidly in armies and after the war the soldiers spread them among the people. That was the experience of this war. In some of the European armies these diseases disabled more soldiers than did shot and shell. Their effect was equivalent to the wiping out of whole army corps, and since the war the disease has played havoc with some of the European peoples.

The knowledge of such facts led our government, when we entered the war, to take rigid measures to prevent the spread of the venereal diseases in our army. These measures were phenomenally successful. Let us briefly review them:

First, the soldier was kept busy and thereby out of mischief; during his work hours, busy with his training; during his hours of leisure he was given wholesome entertainment.

Secondly, he was forbidden alcoholic drinks and houses of prostitution were banished from his neighborhood.

Thirdly, he was given sex instruction by means of pamphlets, moving pictures, talks from his officers and special lectures. He learned that continence is altogether consonant with health and vigor, whereas he had previously been taught that sexual indulgence was a necessity. He learned

that not only was syphilis a disease he already dreaded, a grave disease, but that gonorrhea, a disease he had been accustomed to look upon lightly, was also grave, sometimes worse than syphilis. This is especially true because of its complications. For instance, 10 per cent. of the cases of gonorrhear in our army had gonorrheal rheumatism, the worst form of rheumatism. He learned also that a man may believe himself to be well while the disease is still lurking in his system and may later infect his wife and children. This sex instruction had a decided influence upon the soldier's conduct.

Finally there is the measure we term prophylaxis, preventive treatment in case the individual exposes himself to infection. This consisted usually of urethral injection of a 2 per cent. silver solution and an external application of a mercurial salve. The order was imperative that the soldier have this treatment in case of exposure. To see that the order was enforced the soldier was examined at least twice a month, and if disease were found and he had not previously applied for treatment he was court-martialled and severely punished.

As I said, these measures were phenomenally successful. As Surgeon-General Blue expressed it, "The venereal rate was lowered below that of any army of any nation in the history of the modern world." But even then the venereal disease in our army was by no means an insignificant matter. It was still the most disabling single factor, in truth more disabling than all other acute diseases together, leaving out influenza and measles. Some figures will give you an idea of this. One week when I had occasion to look up the records of Camp Sherman, there were 1,700 patients in the hospital, and of this number 800 were cases of venereal disease. Between September, 1917, and September, 1918, there were 170,000 cases of venereal disease in our army. But I would not have these figures mislead you as to the efficiency of the campaign against these diseases. Only in the smaller number, about one-sixth of these cases, was the disease contracted after the soldiers entered the army. In the larger number, about five-sixths, the disease was contracted before they entered the service; it was acquired in civil life.

This brings us to the problem we have before us today—what can be done to prevent the disease in civil life. Let us again consider a few of the measures so effective in the army, and first the suppression of houses of prostitution. This measure was very effective in the army. To illustrate this fact I will mention the experience of an army corps in the French corps in the French port, Saint Nezaire, where prostitution flourished. Before the division reached this port its disease had been reduced to the low annual rate of fifty-four per thousand. In Saint Nazaire the rate soon rose to two hundred and one. When this was observed, the houses of prostitution were put beyond the soldiers' reach and the rate fell markedly at once.

We could not expect an equal effect in civil life where there is neither the same discipline nor the same control, but still, good must come, if only from the physical possibilities. A woman in a house of prostitution sometimes has contact with fifty men or more in twenty-four hours, whereas if she must seek her prey on the street she can not find nearly as many victims.

And now as to prophylaxis. That had a great effect in the army. Some figures again will make this clear to you. In one division, where the matter was carefully studied, it was found that of those who had received prophylaxis only one in ninety contracted the disease, whereas one in thirty became infected where this treatment was not applied—a reduction of $66\frac{2}{3}$ per cent. Nevertheless, it is very unlikely that this measure will lessen the prevalence of the disease in the community, and this for two—people will not apply for it, and the time they would apply.

Army experience throws light upon this statement. In our own army, notwithstanding the severe punishment inflicted if the soldier did not apply for the treatment after exposure, from one-fourth to one-third of the men failed to do so. The report of a British surgeon is still more illuminating. According to his report, the treatment was a voluntary matter with the soldiers, but they were offered every facility for its application, and yet not one among some thousands of men made use of it. In civil life, where secrecy is usually desired, there would be still less likelihood of the individual seeking the treatment.

As to time, the usual experience has been that when the treatment is applied immediately, or within an hour, after intercourse, it is almost invariably successful, but that after a number of hours has elapsed it is useless. This brings up the question of self-treatment, the individual being supplied with the necessary remedies and applying them himself immediately after intercourse. If this procedure were a common one there is no doubt that it would increase rather than diminish the amount of venereal disease, for usually it would be applied imperfectly and be no source of protection while the sense of security given would lead many into danger which they would otherwise have shunned. There is extended experience in demonstration of the truth of this statement. Before the war this mode of treatment was in vogue in our navy and it was also tried in the New Zealand expeditionary force in France. In both instances it proved to be a failure.

I have spoken so fully of prophylaxis because there are those who believe that it is *the* means of the control, if not the eradication, of these diseases, whereas unless the facts I have given you are altogether misleading, we can expect little or nothing in this way.

Our government did not discontinue its campaign against the venereal diseases when it discharged its soldiers. Each year since the war Congress has appropriated $2,000,000 for this purpose. This money is divided among

the states, which will provide an amount equal to that given them, and now in forty-seven states this campaign is carried on, the national, state and local health authorities working together. So far their effort has been devoted chiefly to finding and curing existing cases of disease. Venereal disease is very contagious. It is catching from person to person. If every case could be cured there would be no further source of contagion and the disease would vanish from the earth. This is a practical impossibility, but to the extent that cases are cured is the prevalence of the disease lessened or at least its increase diminished.

One of the greatest obstacles to finding and curing cases of the disease is the quack and quack nostrums. The only object of the quack is to make money, and to do so he deceives the people. His treatment is likely to be inadequate and he is likely to lead his patient to believe that he is well, while the disease still lurks in his system with all its possibilities of harm. Durng the war, when man power was of vital importance, England severely punished quacks who treated venereal diseases. One of our states, Alabama, recently enacted a law forbidding the advertising of quack venereal doctors and the advertisement and sale of quack venereal remedies. Many of the best newspapers in the land will not accept any medical advertisements. But to really escape the danger of the quack, the people must have a full understanding of the matter. They must know that the quack is a source of harm, whatever disease he pretends to cure, and though he be graduated physician, that he deceives the people, that he plays upon their fears and often falsely arouses fear, that every advertising medical man is a quack and most advertised medicines quack nostrums.

One of the great purposes of this national campaign is to tell about the quack. Another measure is the establishment of free clinics for the treatment of those unable to pay. Here they are given the most modern methods of treatment and are urged to continue the treatment until they are quite well. Also lectures are given to the people in factories and many other places. The lectures aim to tell about the venereal diseases, their danger, their contagiousness, and the great need of avoiding them. They also urge the diseased to go only to competent men for treatment and to remain under treatment until cured and no longer a danger to others.

Many laws have been enacted to help along this campaign. Most states require that physicians report all their cases of venereal disease. This is essential if the campaign is to be successful, for there can scarcely be a sucessful fight against a disease without some idea of its degree of prevalance. Many states require physicians to hand their patients printed instructions how to avoid giving the disease to others, and if these instructions are not heeded health authorities have the power to quarantine the patient. Many states have made so-called eugenic laws, laws to control marriage, to forbid the marriage of infected individuals.

There is a great difference between making laws and enforcing them. Certainly it is a difficult matter to get physicians to report their cases,

almost the foundation-stone of this whole structure. We cannot tell of the future, but we can say that the full success of this campaign will depend upon national, state and local health officials, as well as physicians and voluntary associations established for the purpose, working together and upon an informed and sympathetic public sentiment.

The question arises whether this campaign, now going on nearly two years, has lessened the cases of venereal disease. Probably not. There is much that militates against it, especially the prevailing tone of society. We are feeling something of that moral laxity which always follows war. Some weeks ago we were informed that our dances are 30 per cent. more immoral than they were one year ago, and 150 per cent. more immoral than ten years ago, and there is much more which points the same way. Nevertheless, we can not question that this campaign has done good, if not in lessening the actual number of cases, in preventing such an increase as might otherwise have taken place.

When society has assumed its normal tone, if the campaign is conducted on the lines I have just indicated, it will achieve great results. But even then one must not expect too much; even then there would still be a lamentable amount of venereal disease. To bring this anywhere near the vanishing point something more radical is necessary. This something is education. It is true much has already been done by means of lectures, already mentioned, and the results have been good. But the education I have in mind is more than that. It is the education that can be given to all and at a time of life when harm has not yet been done and when it can influence the whole life. I am alluding, of course, to the sex education of the young. This means essentially education in the home.

All the testimony we have points to the value of this teaching. Questionnaires here and there have brought out that the results are always good. But there is comparatively little such teaching. An inquiry among thousands of college men revealed that only 4 per cent of them had been taught at home, and Dr. Richards, a high school teacher of girls in Philadelphia, stated that only from $\frac{1}{2}$ to 2 per cent. of her girls had received any sex instruction in their own homes.

You know the usual mode of sex instruction: The child gets it on the street and gets bad and perverted ideas. On account of the way it is taught and because its questions receive the harsh word at home, it is led to look upon these matters as shameful, and so is separated from its parents. In a way, it leads a secret life. When the boy gets older he is taught by the gang that sexual indulgence is necessary for health. This and like influences lead him to an illicit sexual life.

The teaching should be just the opposite to this. It should be in the home. The parents should be the teachers; of the growing child, the mother. The teaching should be according to the child's age and needs, beginning when its curiosity is aroused and it asks questions. It should be done in such a

manner as to arouse a reverent spirit in the child. It should be led not to discuss the matter with others, but to always come to the mother when it wants information of this kind and to make of her an utter confidant.

Taught in this way instead of looking upon these things as shameful, it sees the beauty and sanctity of life. It acquires knowledge which safeguards it from many pitfalls. It gets high ideals. Above all, it gets an utter confidant in the mother, often its means of salvation. One can not rate too highly the value to the child of this utter confidant. She is often enabled to safeguard it from impulses in its own heart and from countless corrupting influences about it. It is not so rare that a single child has corrupted a whole group of children or almost a whole school, where a mother, having the confidence of her child, could have prevented the trouble or at least stemmed the tide of corruption. The mother should teach the young child, but, when the boy is older, the father should play his part.

It is because so few parents teach their children that there is demand for sex instruction in the school. This is part of the program of the national campaign against the venereal diseases and really its most important part. But as yet nothing has been done except the beginning of preparation of teachers. Teachers should be thoroughly competent. There is no doubt that unprepared and incompetent teachers can do much harm.

The teaching should begin with the young child. The consensus of opinion is that the child should be led gradually from the knowledge of reproduction in plant and animal to human reproduction and that the teaching should be a part of a general course, such as physiology, biology, domestic science or physical education, so that this knowledge will come to the child almost imperceptibly.

School instructions might be of infinite value, for thereby all children could get the right sex education. Children could get not only knowledge to safeguard them and ideals to elevate them, but also better companions, companions who have also had sex instruction, as well as find less corrupting influences in society, for with universal sex instruction the tone of society would be elevated. Not the least, perhaps the greatest, benefit of school instructions would be that it would prepare a new generation of parents who would give their own children sex instruction.

Just a word more. There are often violent outbreaks of disease, even widespread, where the people can throw all the responsibility upon the health authorities with the assurance, provided due support be given them, that the diseases will be stamped out. Not so the venereal diseases. Health authorities alone can not stamp them out or come anywhere near doing so. The whole responsibility can not be thrust upon them. These are the most widespread, the most menacing of all diseases. They are a world problem and a personal problem. Ought not everyone, ought not each of us, feel and assume his share of that responsibility, a responsibility met by trying to understand the problem and its solution, by his conduct and by his influence?